Synthesis of 1,11-Dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-ones with Potential Topoisomerase I Inhibitory Activity

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Abstract: A series of 1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-ones were prepared by means of Friedländer condensations. The starting materials for the preparations were commercial substituted-2-aminoacetophenones and various 5,6-dihydro-2*H*-indeno[5,6-*d*][1,3]oxazole-2,7(3*H*)-diones that were synthesized from 2(*3H*)-benzoxazolones or their *N*-methyl analogues.

Key words: alkaloids, heterocycles, cyclizations, condensation, fused-ring systems

The natural pentacyclic alkaloid camptothecin (CPT; Figure 1),[1] first isolated from the Chinese tree *Camptotheca acuminata*,[2] acts as a selective poison of the nuclear enzyme topoisomerase I by forming a ternary complex with topoisomerase I and DNA.[3] Stabilization of this complex results in breakdown of DNA by preventing DNA re-ligation.[4] Therapeutic applications of CPT have been hindered by its poor aqueous solubility, and by the severe and unpredictable toxicities identified in early clinical studies performed in the 1970s.[5] Since then, academic and industrial research groups have focussed their attention on the synthesis of the alkaloids of the camptothecin family and their analogues as promising agents for the treatment of human cancers.[6–8]

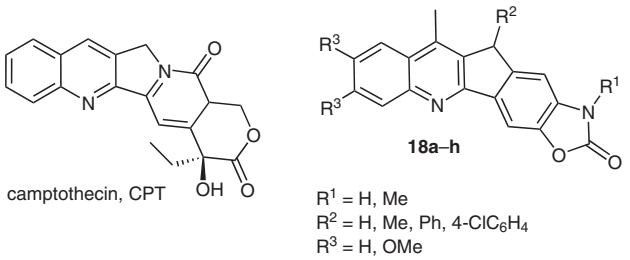

Figure 1 Structures of camptothecin and its analogues **18a–h**

We report the synthesis of a series of new condensed quinolines obtained by a Friedländer-type reaction between an aminoacetophenone, optionally substituted with methoxy groups, and a 5,6-dihydro-*3H*-indeno[5,6-d]oxazole-2,7-dione substituted with methyl and/or aryl groups (Figure 1). These intermediates were synthesized from 2(*3H*)-benzoxazolone (**1**) or its *N*-methyl derivative **2**, both of which are commercially available.

The final products **18a–h** (Figure 1) were synthesized from the intermediates **5–6**, **9**, and **15–17** (Scheme 1). These compounds were synthesized by three routes, starting from 2(*3H*)-benzoxazolone **1** or its *N*-methyl derivative **2** (Scheme 1). Route A, which gave intermediates **5** and **6**, involved two steps. The 2(*3H*)-benzoxazolone **1** or **2** was acylated with 4-chlorobutanoic acid in polyphosphoric acid (PPA)[9] to give oxo alcohols **3** and **4**, which were then cyclized in a mixture of aluminum trichloride and *N*,*N*-dimethylformamide to give the intermediates **5**[10] and **6**.[11] In route B, 3-methyl-2(*3H*)-benzoxazolone (**2**) was acylated in a mixture of aluminum trichloride, *N*,*N*-dimethylformamide, and 3-chloropropanoyl chloride to give chloro ketone **7**,[12] which was dehydrohalogenated with potassium acetate in *N*,*N*-dimethylformamide to give the enone **8**; cyclization of this compound in sulfuric acid gave the indenofurandione **9**. The final route C gave the intermediates compounds **15–17**. The first step involved the acylation of 2(*3H*)-benzoxazolone **1** or **2** by acetic acid in a mixture of aluminum trichloride and *N*,*N*-dimethylformamide to give products **10**[13] and **11**.[14] Crotonization of **10** and **11** with a suitably substituted benzaldehyde was achieved by treatment with potassium hydroxide in ethanol to give the corresponding products **12–14**.[11,15–16] These adducts were cyclized in polyphosphoric acid to give intermediates **15–17**.[11,15,17]

The Friedländer reaction of one of the intermediates **5–6**, **9**, and **15–17** with a commercially available aminoacetophenone, optionally substituted by methoxy groups, gave the corresponding 1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-ones **18a–h**. Two methods were tested: cyclization in acetic acid or cyclization in butanol containing pyridinium 4-toluenesulfonate (Scheme 2).[18] In acetic acid, compounds **18a** and **18e** were obtained in low yields (45 and 55%, respectively), whereas higher yields of these compounds were obtained in butanol (70 and 80%, respectively). The reaction in butanol was therefore used to synthesize the final products **18a–h**.

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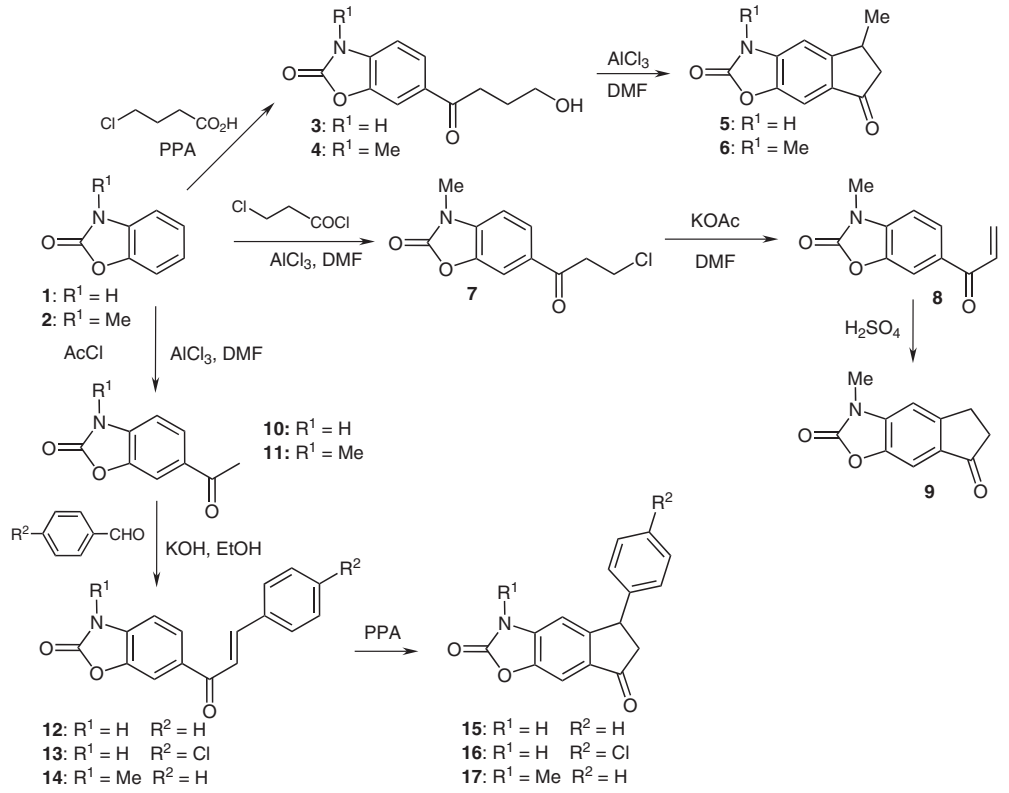
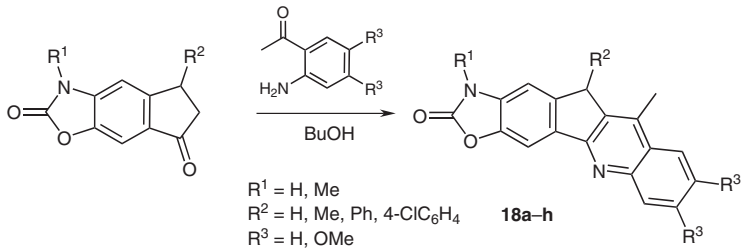


Scheme 1 Synthesis of intermediates **5**–**6**, **9**, and **15**–**17**



Scheme 2 Synthesis of final compounds 1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-b]quinolin-2-ones **18a–h**

Table 1 1,11-Dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-b]quinolin-2-ones **18a–h**

18	R^1	R^2	R^3
a	H	Me	OMe
b	Me	Me	OMe
c	Me	H	OMe
d	H	Ph	H
e	H	Ph	OMe
f	H	4-ClC_6H_4	H
g	H	4-ClC_6H_4	OMe
h	Me	Ph	OMe

The effects of compounds **18a–h** on the proliferation of DU145 human androgen-independent prostate cancer cells were assayed in triplicate by using a standard incubation time of 72 h. Compounds **18a**, **18f**, and **18d** and showed a weak activity, with an inhibition of proliferation of 5% at 10 M, whereas compounds **18b**, **18c**, **18e**, **18g**, and **18h** showed no activity with these resistant cells at this concentration. These results could be the result of several factors, such as the poor solubility of the compounds tested and their poor cellular uptake, which is related to their high values of logP, which were calculated theoretically to be between 3.7 ± 0.4 and 5.6 ± 0.4.

In conclusion, we synthesized a series of 1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-b]quinolin-2-ones **18a–h** by a Friedländer-type reaction. The antiproliferative activities of these compounds were examined, and these studies merit further investigation in a solvent other than dimethyl sulfoxide, for example, *N*,*N*-dimethylacetamide. Studies to improve the potential cytotoxic activity of compounds **18a–h** are underway. Furthermore, modifications of the structures of the compounds by adding an ionizable moiety, such as an alkylamine chain or cycloalkylamine, are in progress.

Compounds were purified on a glass column by using Merck silica gel 60 (230–400 mesh). Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. IR spectra were recorded in KBr disks over the range 500–4000 cm^{-1} on a Nicolet 550-FT spectrometer. ^1H and ^{13}C NMR proton spectra were recorded on a Bruker AVANCE 300 spectrometer, and chemical shifts are reported in ppm relative to TMS as an internal standard. Mass spectra were recorded on a quadrupolar Finnigan MAT SSQ 710 instrument.

6-Acryloyl-3-methyl-2(*3H*)-benzoxazolone (8)
KOAc (3.9 g, 37.5 mmol) was added to a soln of benzoxazolone **7** (9.0 g, 37.5 mmol) in DMF (150 mL), and the mixture was warmed to 75–80 °C for 1 h. The mixture was hydrolyzed with cold H_2O (250 mL) and then stirred for 30 min. The precipitate was filtered off, washed with H_2O, and recrystallized (toluene); yield: 64%; mp 148–149 °C

IR (KBr): 1777, 1655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.48 (s, 3 H, CH_3), 5.96 (dd, *J* = 10.5, 1.8 Hz, 1 H, CH), 6.49 (dd, *J* = 16.9 Hz, 1.8 Hz, 1 H, CH), 7.08 (d, *J* = 8.2 Hz, 1 H, H_4), 7.19 (dd, *J* = 16.9, 10.5 Hz, 1 H, CH), 7.85 (d, *J* = 1.5 Hz, 1 H, H_7), 7;87 (d, *J* = 8.2 Hz, *J* = 1.5 Hz, 1 H, H_5).

MS (EI, 70 eV): *m/z* (%) = 204.4 [M^+ + 1].

3-Methyl-5,6-dihydro-2*H*-indeno[5,6-*d*][1,3]oxazole-2,7(3*H*)-dione (9)
Benzoxazolone **8** (2.6 g, 13 mmol) was added to a soln of concd H_2SO_4 (96%; 50 mL) and the soln was warmed to 60 °C for 3 h. The mixture was carefully hydrolyzed with cold H_2O (100 mL) and stirred for 1 h. The precipitate was filtered off, washed with H_2O, and recrystallized (toluene); yield: 25%; mp 225–226 °C.

IR (KBr): 1778, 1696 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.65 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.12 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.34 (s, 3 H, CH_3), 7.43 (s, 1 H, H_{Ar}), 7.49 (s, 1 H, H_{Ar}).

MS (EI, 70 eV): *m/z* (%) = 204.1 [M^+ + 1].

Compounds 18a–h; General Procedure
A mixture of the appropriate intermediate (3.8 mmol), a 2-aminoacetophenone (5.6 mmol), and PPTS (1.42 g, 5.6 mmol) in BuOH (10 mL) was refluxed in a Dean–Stark apparatus for 4 h and then cooled to r.t. The precipitate was filtered off, washed with H_2O and Et_2O, and recrystallized.

7,8-Dimethoxy-10,11-dimethyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18a)
Yellow crystals (MeOH–DMF, 3:1); yield: 70%; mp > 250 °C.

IR (KBr): 3210, 1784, 1641 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.79 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.10 (s, 3 H, CH_3), 4.24 (s, 6 H, OCH_3), 4.54 (d, *J* = 6.9 Hz, 1 H, CH), 7.60 (s, 1 H, H_{Ar}), 7.69 (s, 1 H, H_{Ar}), 7.79 (s, 1 H, H_{Ar}), 8.25 (s, 1 H, H_{Ar}), 11.60 (s, 1 H, NH).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 15.1, 19.6, 39.7, 55.5, 56, 102, 103, 106.5, 108.5, 122.2, 132.4, 133.8, 136.5, 137.5, 143.7, 144.6, 147.3, 148.9, 151.7, 155, 157.3.

MS (EI, 70 eV): *m/z* (%) = 363.6 [M^+ + 1].

7,8-Dimethoxy-1,10,11-trimethyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18b)
Yellow crystals (MeOH–DMF, 3:1); yield: 45%; mp > 250 °C.

IR (KBr): 1765, 1646 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.80 (d, *J* = 6.9 Hz, 3 H, H_3), 3.11 (s, 3 H, CH_3), 3.68 (s, 3 H, CH_3), 4.24 (s, 6 H, CH_3), 4.56 (d, 1 H, CH, *J* = 6.9 Hz), 7.55 (m, 2 H, H_{Ar}), 7.69 (s, 1 H, H_{Ar}), 8.23 (s, 1 H, H_{Ar}).

^{13}C NMR (300 MHz, TFA-d_6): δ = 15, 16.7, 27.6, 41.1, 55.6, 56, 99.3, 103.6, 104.4, 105.8, 108.8, 120.1, 123.3, 125.9, 133.7, 136.7, 138.4, 143.2, 150.3, 151.5, 155.4, 157.23.

MS (EI, 70 eV): *m/z* (%) = 377.2 [M^+ + 1].

7,8-Dimethoxy-1,10-dimethyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18c)
Yellow crystals (MeOH–DMF, 3:1); yield: 60%; mp > 250 °C.

IR (KBr): 1766, 1643 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.47 (s, 3 H, CH_3), 3.10 (s, 3 H, CH_3), 3.66 (s, 6 H, OCH_3), 3.78 (s, 2 H, CH_2), 7.02 (s, 1 H, H_{Ar}), 7.05 (s, 1 H, H_{Ar}), 7.12 (s, 1 H, H_{Ar}), 7.68 (s, 1 H, H_{Ar}).

^{13}C NMR (300 MHz, TFA-d_6): δ = 14.9, 27.5, 33.7, 55.6, 56, 99.4, 103.5, 104.5, 106.7, 108.8, 120.1, 122.9, 127.6, 133.9, 136.6, 143.2, 145, 150.7, 151.3, 155.6, 157.2.

MS (EI, 70 eV): *m/z* (%) = 363.3 [M^+ + 1].

1-Methyl-11-phenyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18d)
Yellow crystals (MeOH–DMF, 3:1); yield: 50%; mp > 250 °C.

IR (KBr): 3256, 1778, 1648 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.16 (s, 3 H, CH_3), 5.48 (s, 1 H, CH), 6.93 (s, 1 H, H_{Ar}), 7.12 (d, *J* = 6.4 Hz, 2 H, H_{Ar}), 7.32 (m, 3 H, H_{Ar}), 7.57 (dd, *J* = 7.0, 1.2 Hz, 1 H, H_{Ar}), 7.74 (dd, *J* = 8.5, 1.2 Hz, 1 H, H_{Ar}), 7.92 (s, 1 H, H_{Ar}), 8.11 (m, 2 H, H_{Ar}), 11.83 (br s, 1 H, NH).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 14.9, 50.7, 102.8, 106.9, 124.5, 126, 127.4, 127.8, 128.1, 128.7, 129.4, 129.8, 130.5, 133.1, 133.5, 137.1, 137.5, 139.2, 141.4, 143.9, 147, 148.5, 154.8, 160.4.

MS (EI, 70 eV): *m/z* (%) = 365.5 [M^+ + 1].

7,8-Dimethoxy-10-methyl-11-phenyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18e)
Yellow crystals (MeOH–DMF, 3:1); yield: 80%; mp > 250 °C.

IR (KBr): 3300, 1785, 1644 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.31 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 5.38 (s, 1 H, CH), 6.90 (s, 1 H, H_{Ar}), 7.10 (d, *J* = 7.1 Hz, 2 H, H_{Ar}), 7.29 (m, 4 H, H_{Ar}), 7.46 (s, 1 H, H_{Ar}), 7.80 (s, 1 H, H_{Ar}), 11.75 (br s, 1 H, NH).

^{13}C NMR (300 MHz, TFA-d_6): δ = 15.1, 52.5, 55.7, 56.1, 99.5, 103.6, 104.6, 108.9, 109.3, 120.1, 123.6, 126.1, 127.3, 128.5, 129.7, 134.3, 134.5, 136.1, 137.5, 144.4, 150.1, 150.9, 151.8, 151.9, 155.9, 158.

MS (EI, 70 eV): *m/z* (%) = 425.6 [M^+ + 1].

11-(4-Chlorophenyl)-10-methyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18f)
Yellow crystals (DMF); yield: 50%; mp > 250 °C.

IR (KBr): 3332, 1748, 1652 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.38 (s, 3 H, CH_3), 5.53 (s, 1 H, CH), 6.95 (s, 1 H, H_{Ar}), 7.15 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.35 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.57 (dd, *J* = 7.0, 1.2 Hz, 1 H, H_{Ar}), 7.75 (dd, *J* = 8.5, 1.2 Hz, 1 H, H_{Ar}), 7.92 (s, 1 H, H_{Ar}), 8.05 (m, 2 H, H_{Ar}), 11.74 (br s, 1 H, NH).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 14.9, 49.8, 102.7, 106.8, 124.4, 125.9, 127.3, 129.4, 129.7, 130.1, 130.6, 131.2, 131.9, 133.2, 133.4, 136.7, 136.9, 139.6, 140.5, 143.9, 146.4, 148.2, 154.8, 160.3.

MS (EI, 70 eV): *m/z* (%) = 399.7 [M^+ + 1].

11-(4-Chlorophenyl)-7,8-dimethoxy-10-methyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18g)
Yellow crystals (DMF); yield: 70%; mp > 250 °C.

IR (KBr): 3095, 1763, 1647 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.53 (s, 3 H, CH_3), 4.43 (s, 3 H, OCH_3), 4.52 (s, 3 H, OCH_3), 5.32 (s, 1 H, CH), 6.91 (d, 2 H, H_{Ar}, *J* = 8.4 Hz), 7.20 (d, 2 H, H_{Ar}, *J* = 8.4 Hz), 7.31 (s, 1 H, H_{Ar}), 7.42 (s, 1 H, H_{Ar}), 7.45 (s, 1 H, H_{Ar}), 8.11 (s, 1 H, H_{Ar}), 11.53 (br s, 1 H, NH).

^{13}C NMR (300 MHz, TFA-d_6): δ = 15.1, 51.6, 55.7, 56.1, 99.5, 103.6, 104.7, 108.8, 109.1, 120.1, 123.6, 126.1, 128.6, 129.8, 134.3, 134.6, 134.8, 134.9, 136.8, 144.4, 150.1, 150.9, 151.6, 151.7, 155.9, 157.8.

MS (EI, 70 eV): *m/z* (%) = 459.8 [M^+ + 1].

7,8-Dimethoxy-1,10-dimethyl-11-phenyl-1,11-dihydro-2*H*-[1,3]oxazolo[4′,5′:5,6]indeno[1,2-*b*]quinolin-2-one (18h)
Yellow crystals (MeOH–DMF, 3:1); yield 40%; mp > 250 °C.

IR (KBr): 1782, 1645 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.71 (s, 3 H, CH_3), 3.55 (s, 3 H, CH_3), 4.19 (s, 3 H, OCH_3), 4.24 (s, 3 H, OCH_3), 5.54 (s, 1 H, CH), 7.15 (m, 2 H, H_{Ar}), 7.28 (s, 1 H, H_{Ar}), 7.38 (m, 3 H, H_{Ar}), 7.62 (d, *J* = 7.1 Hz, 2 H, H_{Ar}), 8.27 (s, 1 H, H_{Ar}).

^{13}C NMR (300 MHz, DMSO-d_6): δ = 14.9, 27.5, 52.5, 55.6, 56, 99.4, 103.6, 104.3, 106.9, 108.8, 112.6, 116.3, 120, 123.5, 126, 127.4, 128.5, 129.6, 134.1, 136.2, 136.9, 137.5, 143.4, 150.8, 151.8, 155.8, 157.2.

MS (EI, 70 eV): *m/z* (%) = 438.3 [M^+ + 1].

Cell Culture and Cell Proliferation Assay
Human prostate DU145 cancer cells were grown at 37 °C in RPMI 1640 medium supplemented with 10% fetal calf serum, in a humidified incubator under 5% CO_2. In the cell-proliferation assay, cells were plated (3200 cells/well) on 96-well plates. After 3 days, the cell medium was changed to serum-free medium, and the cells were starved for 24 h for culture synchronization. Cells were then incubated in a culture medium that contained 10 M of the test compound dissolved in less than 0.1% DMSO. After incubation for 72 h, cell growth was estimated by means of the colorimetric MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] test.

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References

(1) Dallavalle, S.; Merlini, L. In *Modern Alkaloids*; Fattorusso, E.; Tagliatatela, O., Eds.; Wiley-VCH: Weinheim, **2008**, 503.
(2) Wall, M. E.; Wani, M. C.; Cooke, C. E.; Palmer, K. T.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.
(3) Hsiang, Y. H.; Hertzberg, R.; Hetch, S. M.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873.
(4) Special issue: The Camptothecins: Unfolding Their Anticancer Potential, *Ann. N. Y. Acad. Sci.* **2000**, *922*, 1
(5) Moertel, C. G.; Schutt, A. J.; Reitemeier, R. J.; Hahn, R. G. *Cancer Chemother. Rep.* **1972**, *56*, 649.
(6) Feng, W.; Satyanarayana, M.; Tsai, Y.-c.; Liu, A. A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3570.
(7) Nacro, K.; Zha, C.; Guzzo, P. R.; Herr, R. J.; Peacec, D.; Friedrichc, T. D. *Bioorg. Med. Chem.* **2007**, *15*, 4237.
(8) Cheng, Y.; An, L. K.; Wu, N.; Wang, X. D.; Bu, X. Z.; Huang, Z. S.; Gu, L. Q. *Bioorg. Med. Chem.* **2008**, *16*, 4617.
(9) Poupaert, J. H.; Kanyonyo, M.; Ucar, H.; Mouithys, A. M.; Diouf, O.; Lesieur, D. *Bull. Soc. Chim. Belg.* **1996**, *105*, 397.
(10) Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Henichart, J. P. *Bull. Soc. Chim. Belg.* **1992**, *101*, 1053.
(11) Merdji, B.; Lesieur, D.; Lespagnol, C.; Barbry, D.; Couturier, D. *J. Heterocycl. Chem.* **1981**, *18*, 1223.
(12) Aichaoui, H.; Lesieur, D.; Henichart, J. P. *J. Heterocycl. Chem.* **1992**, *29*, 171.
(13) Aichaoui, H.; Poupaert, J. H.; Lesieur, D.; Henichart, J. P. *Tetrahedron* **1991**, *47*, 6649.
(14) Moussavi, Z.; Lesieur, D.; Lespagnol, C.; Sauzières, J.; Olivier, P. *Eur. J. Med. Chem.* **1989**, *24*, 55.
(15) Depreux, P.; Aichaoui, H.; Lesieur, I. *Heterocycles* **1993**, *36*, 1051.
(16) Merdji, B.; Lesieur, D.; Lespagnol, C.; Barbry, D.; Couturier, D. *J. Heterocycl. Chem.* **1981**, *18*, 1223.
(17) Park, C. H.; Siomboing, X.; Yous, S.; Gressier, B.; Luyckx, M.; Chavatte, P. *Eur. J. Med. Chem.* **2002**, *37*, 461.
(18) Chackal, S.; Houssin, R.; Henichart, J. P. *J. Org. Chem.* **2002**, *67*, 3502.