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Modular *o*-Quinone Catalyst System for Dehydrogenation of Tetrahydroquinolines under Ambient Conditions

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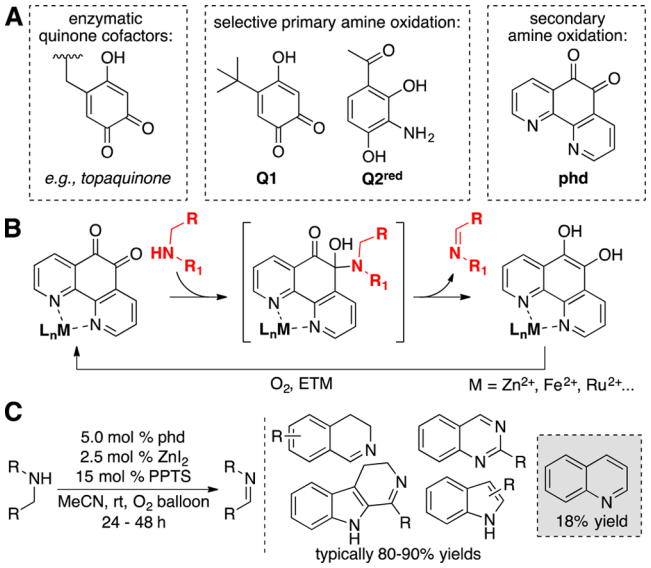
Supporting Information

ABSTRACT: Quinolines are common pharmacophores present in numerous FDA-approved pharmaceuticals and other bioactive compounds. Here, we report the design and development of new *o*-quinone-based catalysts for the oxidative dehydrogenation of tetrahydroquinolines to afford quinolines. Use of a Co(salophen) cocatalyst allows the reaction to proceed efficiently with ambient air at room temperature. The utility of the catalytic method is demonstrated in the preparation of a number of medicinally relevant quinolines.

Copper amine oxidases contain a tyrosine-derived *o*-quinone in their active site that mediates aerobic oxidation of primary amines to aldehydes (e.g., topaquinone, Scheme 1A).[1] Biomimetic *o*-quinones such as **Q1** and **Q2** (Scheme 1A; $\mathbf{Q2}^{red}$ is proposed to form an *o*-quinone in situ) have been shown to be effective synthetic catalysts for aerobic dehydrogenation of primary amines, typically affording homocoupled imines.[2] Both topaquinone and the biomimetic quinone catalysts mediate amine oxidation via a "trans-amination" pathway, initiated by formation of an imine adduct of the substrate with the quinone. This mechanism accounts for the highly selective oxidation of primary over secondary and tertiary amines. We recently reported that 1,10-phenanthroline-5,6-dione (phd, Scheme 1A) promotes amine oxidation by a non-biomimetic "addition–elimination" pathway involving a hemiaminal intermediate (Scheme 1B).[3] This novel mechanism enabled the substrate scope to be expanded to include secondary amines. Aerobic dehydrogenation of a number of different nitrogen heterocycles was achieved by using phd in combination with ZnI_2 and pyridinium *p*-toluenesulfonate (PPTS) as a cocatalyst (Scheme 1C).

This phd/ZnI_2 catalyst system demonstrated the feasibility of aerobic secondary amine dehydrogenation, but reactions often required up to 48 h to reach completion and certain product classes were not accessible. For example, quinolines are an important class of heterocycles, but even the parent tetrahydroquinoline underwent dehydrogenation to quinoline in only 18% yield (Scheme 1C). Here, we describe an octahedral $[Ru(phd)_3]^{2+}$ catalyst that shows considerably higher activity for amine oxidation, including successful aerobic dehydrogenation of diverse tetrahydroquinolines at room temperature with ambient air as the source of O_2.[4] This work highlights the modular nature of the phd *o*-quinone catalyst that makes it readily amenable to optimization and adaptation to different applications. Replacement of iodide with Co(salophen) (salophen = *N*,*N*′-bis(salicylidene)-1,2-phenylenediamine) as a redox cocatalyst contributes significantly to the efficiency of the reactions.

Scheme 1. *o*-Quinone-Catalyzed Dehydrogenation of Saturated C–N Bonds



In our initial studies, we compared the previously optimized phd/ZnI_2 catalyst system with simple octahedral $[Fe(phd)_3]^{2+}$ and $[Ru(phd)_3]^{2+}$ complexes in the oxidation of tetrahydroquinoline to quinoline (Figure 1). The time course traces (Figure 1) show the low activity and conversion of the previously reported phd/ZnI_2 catalyst (red trace); the catalyst loses activity ~6–7 h into the reaction after reaching ≤20% conversion to the quinoline product. The Fe and Ru complexes (2.5 mol %) were also tested (green and blue traces, respectively). The use of Bu_4NI (1 mol %) as a cocatalyst reflected previous observations showing that the I^-/I_3^- redox couple promotes aerobic oxidation of the reduced, hydroquinone form of the phd catalyst.[5] $[Fe(phd)_3]^{2+}$ showed a similar initial rate to the ZnI_2 catalyst, but it exhibited somewhat improved stability. In contrast, $[Ru(phd)_3]^{2+}$ exhibited a significant increase in activity and a 93% yield of quinoline was obtained after 24 h. On the basis of this result, we characterized $[Ru(phd)_3](ClO_4)_2$ via X-ray crystallography (Figure 2).[6,7]

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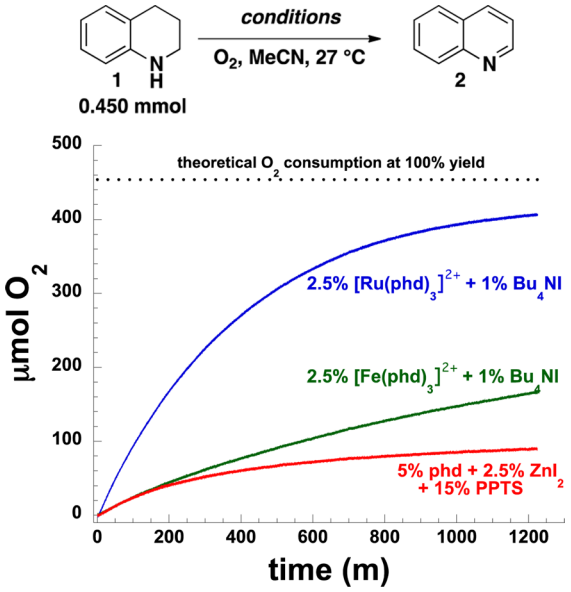


Figure 1. Rate comparison of Zn-, Fe-, and Ru-based catalyst systems in the oxidation of tetrahydroquinoline to quinoline.

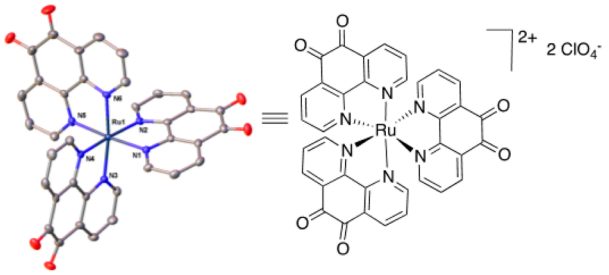
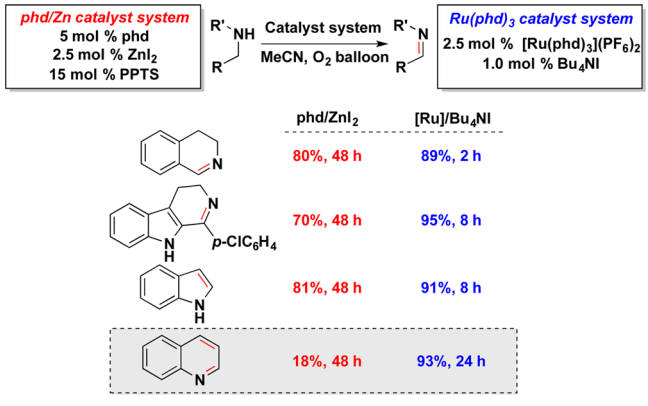


Figure 2. X-ray crystal structure of $[Ru(phd)_3](ClO_4)_2$ shown with 50% probablility elipsoids. All H atoms and acetonitrile solvent molecules are omitted for clarity (see Supporting Information).

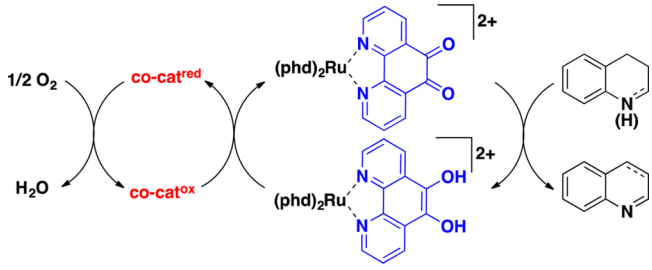
This $[Ru(phd)_3]^{2+}/Bu_4NI$ catalyst was tested with a series of challenging *N*-heterocyclic substrates that had required 48 h to reach completion with the phd/ZnI_2 catalyst (Scheme 2). Improved yields and significantly decreased reaction times were observed in each case, with the most dramatic improvement observed in the dehydrogenation of tetrahydroquinoline.

Iodide was previously shown to mediate aerobic oxidation of the reduced hydroquinone form of the catalyst, and a catalytic

Scheme 2. Aerobic *N*-Heterocycle Dehydrogenation with phd/ZnI_2 and $[Ru(phd)_3](PF_6)_2/Bu_4NI$ Catalyst Systems



Scheme 3. Proposed Catalytic Sequence for $[Ru(phd)_2]^{2+}$-Mediated Dehydrogenation of Tetrahydroquinolines



sequence for the present dehydrogenation reactions is depicted in Scheme 3, where Co-$Cat^{red/ox}$ = $3I^-/I_3^-$. (It is not known whether dehydrogenation of the intermediate dihydroquinoline involves the catalyst.) We speculated that alternative cocatalysts could lead to even better catalytic reactivity. Bäckvall and others have highlighted the role of cocatalysts for aerobic oxidation of benzoquinone in multicomponent catalytic reactions,[8,9] and molecular catecholase mimics have been identified for aerobic oxidation of hydroquinones.[10] Drawing on these precedents, we tested a number of possible cocatalysts as replacements for Bu_4NI, including Cu(pc), Fe(pc), Co(salophen), and Co(salpr) (pc = phthalocyanine; salpr = bis(salicylideneiminato-3-propyl)methylamine).[11] Co(salophen) proved to be particularly effective, enabling full conversion within 3 h (Figure 3).[12]

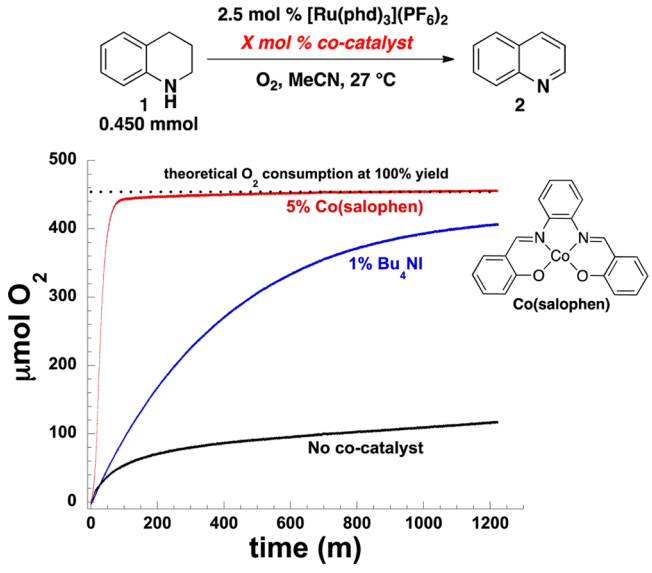


Figure 3. Rate comparison of different cocatalysts on the $Ru(phd)_3$-catalyzed aerobic oxidation of tetrahydroquinoline.

Subsequent studies showed that Co(salophen) enabled the reactions to proceed efficiently under ambient conditions (at room temperature with ambient air as the oxidant). The $[Ru(phd)_3]^{2+}$ catalyst structurally resembles Ru-polypyridyl complexes commonly used as photoactive catalysts, but control experiments show that the reactions exhibit identical behavior in the presence and absence of light.[13] In addition, no reaction was observed in the absence of $[Ru(phd)_3]^{2+}$, suggesting that Co(salophen) is not a competent dehydrogenation catalyst under these conditions.

This catalyst system was then demonstrated in the dehydrogenation of a number of other tetrahydroquinolines

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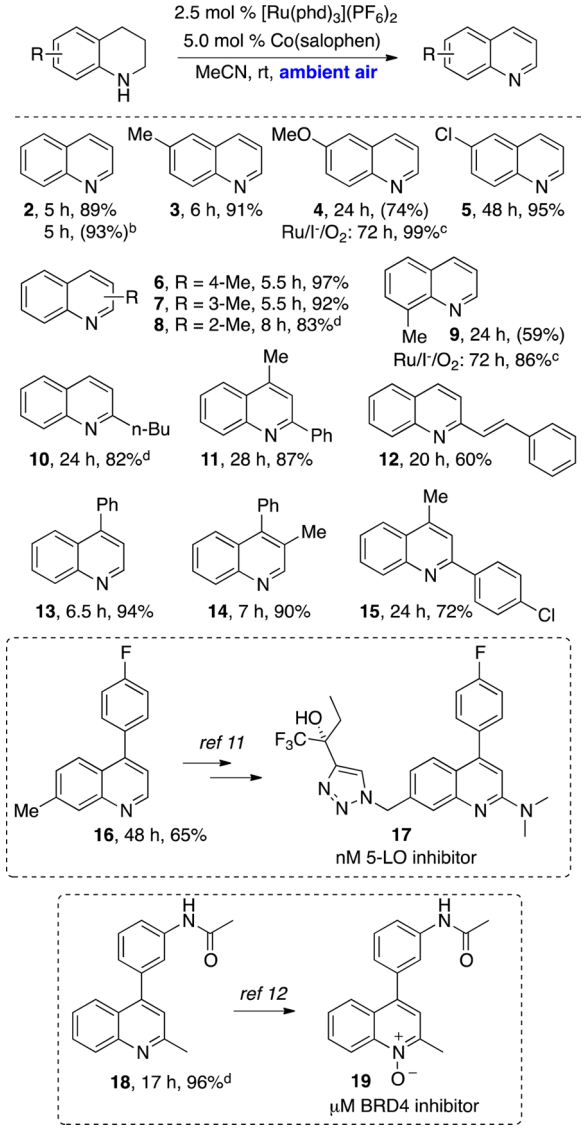
(Table 1). 6-Methylquinoline **3** was obtained cleanly after 6 h (91% yield), but the more-electron-rich 6-methoxyquinoline **4** was isolated in only 74% yield and considerable side-product formation was observed. Excellent yields of this product could be obtained when the reaction was carried out using 1.0 mol % Bu_4NI as the cocatalyst, suggesting that Co(salophen) cocatalyst contributes to side product formation in this reaction. The electron-deficient 6-chloroquinoline **5** was obtained in excellent yield (95%) with the original $[Ru(phd)_3]^{2+}$/Co(salophen) catalyst system.

Substitution at the 2, 3, and 4 positions was well-tolerated: 4-methylquinoline **6** (97%) and 3-methylquinoline **7** (92%) were obtained after short reaction times (5−6 h). The sterically hindered 2-methylquinoline **8** (83%) was obtained after slightly longer reaction time if MeOH was used as the solvent instead of MeCN.[14] Other effective 2-substituted tetrahydroquinoline substrates included 2-butyl, 2-phenyl, and 2-styrenyl derivatives, affording quinolines **10**, **11**, and **12** in 82%, 87%, and 60% yields, respectively. The medicinally relevant 4-(*p*-fluorophenyl)-7-methylquinoline **16**, an intermediate en route to nM 5-lipoxygenase inhibitor[15] **17**, was obtained in 65% yield, and the advanced intermediate **18** toward BRD4 inhibitor[16] **19** was obtained in 96% yield.

When probing the reactivity of polycyclic substrate **20** (Scheme 4), both dehydrogenation and benzylic oxygenation occurred to afford product **21** in 68% isolated yield. This reaction provides concise access to the indeno[2,1-*c*]quinoline substructure present in numerous biologically active compounds,[17] including antiprotozoal agent **22**[18] and phase II topoisomerase inhibitor TAS-103.[19]

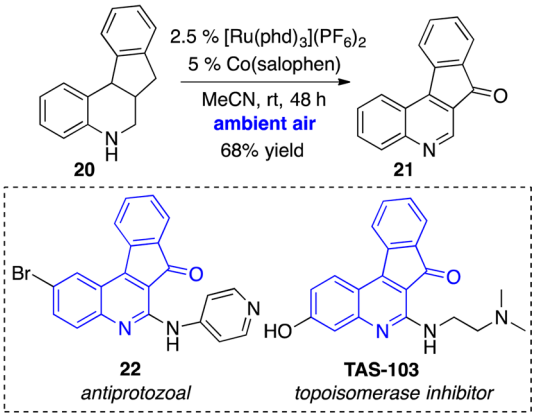
In conclusion, these results demonstrate the utility of $[Ru(phd)_3]^{2+}$ as a novel *o*-quinone catalyst for dehydrogenation of *N*-heterocycles. The results show that the substitutionally inert Ru^{2+} ion is more effective than Zn^{2+} in activating phd toward secondary amine dehydrogenation. Replacement of iodide with Co(salophen) as a redox cocatalyst to promote aerobic oxidation of the hydroquinone catalyst leads to substantial improvement in catalyst activity and enables the reactions to proceed under ambient conditions. The modular nature of the catalyst system described here has important implications for future studies targeting other aerobic quinone-mediated oxidation reactions.

Table 1. Substrate Scope[a]



[a]Conditions: tetrahydroquinoline (1.0 mmol), $[Ru(phd)_3](PF_6)_2$ (25.5 mg, 0.025 mmol), Co(salophen) (18.7 mg, 0.05 mmol) in MeCN (4.0 mL), air, rt. Isolated yields (yields in parentheses determined by ^1H NMR). [b]Performed in the dark. [c]Standard conditions, but Bu_4NI (3.7 mg, 0.01 mmol) used instead of Co(salophen) and 1 atm O_2 instead of air. [d]MeOH solvent.

Scheme 4. Synthesis of Indeno[2,1-*c*]quinoline 21[a]



[a]Reactions conditions: tetrahydroquinoline **20** (221.3 mg, 1.0 mmol), $Ru(phd)_3(PF_6)_2$ (25.5 mg, 0.025 mmol), Co(salophen) (18.7 mg, 0.05 mmol) in MeCN (4.0 mL), stirring under air balloon at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data for all products, and additional screening data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Klinman, J. P. *J. Biol. Chem.* **1996**, *271*, 27189. (b) Mure, M. *Acc. Chem. Res.* **2004**, *37*, 131.

(2) (a) Wendlandt, A. E.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 2850. (b) Largeron, M.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5409. (c) Largeron, M.; Fleury, M.-B. *Science* **2013**, *339*, 43.

(3) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 506.

(4) For leading references to other catalytic methods for dehydrogenation of tetrahydroquinolines, see: (a) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480. (b) Yamaguchi, R.; Ikeda, C.; Takahashi, Y.; Fujita, K.-i. *J. Am. Chem. Soc.* **2009**, *131*, 8410. (c) Wu, J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6983. (d) Chakraborty, S.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 8564.

(5) Through reaction screening, it was determined that 1.0 mol % Bu_4NI was optimal in the case of both the Fe and Ru catalysts. See Supporting Information for additional details.

(6) For examples of homo- and heteroleptic Ru-phd complexes, see: (a) Nguyen, F.; Anson, F. C. *Electrochim. Acta* **1998**, *44*, 239. (b) Poteet, S. A.; Majewski, M. B.; Breitbach, Z. S.; Griffith, C. A.; Singh, S.; Armstrong, D. W.; Wolf, M. O.; MacDonnell, F. M. *J. Am. Chem. Soc.* **2013**, *135*, 2419. (c) Poteet, S. A.; MacDonnell, F. M. *Dalton Trans.* **2013**, *42*, 13305. (d) Parakh, P.; Gokulakrishnan, S.; Prakash, H. *Sep. Purif. Technol.* **2013**, *109*, 9.

(7) Ru-phd complexes have been applied previously as catalysts for NADH oxidation: (a) Goss, C. A.; Abruña, H. D. *Inorg. Chem.* **1985**, *24*, 4263. (b) Hilt, G.; Steckhan, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1706. (c) Rivera, N.; Colón, Y.; Guadalupe, A. R. *Bioelectrochem. Bioenerg.* **1994**, *34*, 169. (d) Wu, Q.; Maskus, M.; Pariente, F.; Tobalina, F.; Fernández, V. M.; Lorenzo, E.; Abruña, H. D. *Anal. Chem.* **1996**, *68*, 3688. (e) Hilt, G.; Lewall, B.; Montero, G.; Utley, J. H. P.; Steckhan, E. *Liebigs Ann.* **1997**, 2289. (f) Hilt, G.; Jarbawi, T.; Heineman, W. R.; Steckhan, E. *Chem.—Eur. J.* **1997**, *3*, 79. (g) Yokoyama, K.; Ueda, Y.; Nakamura, N.; Ohno, H. *Chem. Lett.* **2005**, *34*, 1282. (h) Pinczewska, A.; Sosna, M.; Bloodworth, S.; Kilburn, J. D.; Bartlett, P. N. *J. Am. Chem. Soc.* **2012**, *134*, 18022.

(8) For a recent review of this area, see: Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506.

(9) For a specific recent example, see: Volla, C. M. R.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2013**, *52*, 14209.

(10) For leading references, see: (a) Sakamoto, H.; Funabiki, T.; Yoshida, S.; Tarama, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2760. (b) Tsuruya, S.; Yanai, S.-i.; Masai, M. *Inorg. Chem.* **1986**, *25*, 141. (c) Sakata, K.; Kikutake, T.; Shigaki, Y.; Hashimoto, M.; Ogawa, H. I.; Kato, Y. *Inorg. Chim. Acta* **1988**, *144*, 1. (d) Simándi, L. I.; Simándi, T. M.; May, Z.; Besenyei, G. *Coord. Chem. Rev.* **2003**, *245*, 85.

(11) See Supporting Information for details.

(12) The combinations of Co(salophen) with $Zn(OTf)_2$/phd and with the $[Fe(phd)_3]^{2+}$ complex were also tested. Good results were obtained with $Zn(OTf)_2$/phd/Co(salophen); however, the results did not surpass those of $[Ru(phd)_3]^{2+}$/Co(salophen).

(13) Photoexcitation of Ru-phd complexes is typically thought to terminate in non-radiative decay pathways arising from the semiquinone structure. See refs 6b,c.

(14) In general, the use of methanol as a solvent improved yields in the oxidation of 2-substituted tetrahydroquinolines. For other substrates, acetonitrile was the preferred solvent.

(15) (a) Delorme, D.; Dubé, D.; Ducharme, Y.; Grimm, E. L.; Friesen, R.; Lepine, C. (Merck Frosst, Canada). U.S. Pat. 5,552,437, Sept 3, 1996. (b) Grimm, E. L.; Ducharme, Y.; Frenette, R.; Friesen, R.; Gagnon, M.; Juteau, H.; Laliberte, S.; MacKay, B.; Gareau, Y. (Merck, USA). U.S. Pat. Appl. 2008/0188521 A1, Aug 7, 2008.

(16) Vidler, L. R.; Filippakopoulos, P.; Fedorov, O.; Picaud, S.; Martin, S.; Tomsett, M.; Woodward, H.; Brown, N.; Knapp, S.; Hoelder, S. *J. Med. Chem.* **2013**, *56*, 8073.

(17) See, for example: (a) Upadhayaya, R. S.; Shinde, P. D.; Sayyed, A. Y.; Kadam, S. A.; Bawane, A. N.; Poddar, A.; Plashkevych, O.; Földesi, A.; Chattopadhyaya, J. *Org. Biomol. Chem.* **2010**, *8*, 5661. (b) Upadhayaya, R. S.; Lahore, S. V.; Sayyed, A. Y.; Dixit, S. S.; Shinde, P. D.; Chattopadhyaya, J. *Org. Biomol. Chem.* **2010**, *8*, 2180. (c) Upadhayaya, R. S.; Shinde, P. D.; Kadam, S. A.; Bawane, A. N.; Sayyed, A. Y.; Kardile, R. A.; Gitay, P. N.; Lahore, S. V.; Dixit, S. S.; Földesi, A.; Chattopadhyaya, J. *Eur. J. Med. Chem.* **2011**, *46*, 1306.

(18) Upadhayaya, R. S.; Dixit, S. S.; Földesi, A.; Chattopadhyaya, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2750.

(19) (a) Utsugi, T.; Aoyagi, K.; Asao, T.; Okazaki, S.; Aoyagi, Y.; Sano, M.; Wierzba, K.; Yamada, Y. *Jpn. J. Cancer Res.* **1997**, *88*, 992. (b) Okazaki, S.; Asao, T.; Wakida, M.; Ishida, K.; Washinosu, M.; Utsugi, T.; Yamada, Y. (Taiho Pharmaceutical Co., Japan). Eur. Pat. 0 713 870 B1, July 18, 2001. (c) Fujimoto, S. *Biol. Pharm. Bull.* **2007**, *30*, 1923.