Bioorganic & Medicinal Chemistry Letters 20 (2010) 2335–2339

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Potent and selective inhibition of human cytochrome P450 3A4 by *seco*-pancratistatin structural analogs

James McNulty [a,*], Jerald J. Nair [a], Mohini Singh [b], Denis J. Crankshaw [b], Alison C. Holloway [b]

[a] Department of Chemistry and Chemical Biology, McMaster University, 1280 Main Street West, Hamilton, Ont., Canada L8S 4M1
[b] Department of Obstetrics and Gynecology, McMaster University, 1200 Main Street West, Hamilton, Ont., Canada L8N 3Z5

ARTICLE INFO

Article history:
Received 17 December 2009
Revised 21 January 2010
Accepted 27 January 2010
Available online 4 February 2010

Keywords:
Pancratistatin
Human cytochrome
P450 3A4
Anticancer agent
Antioxidant
Antifungal

ABSTRACT

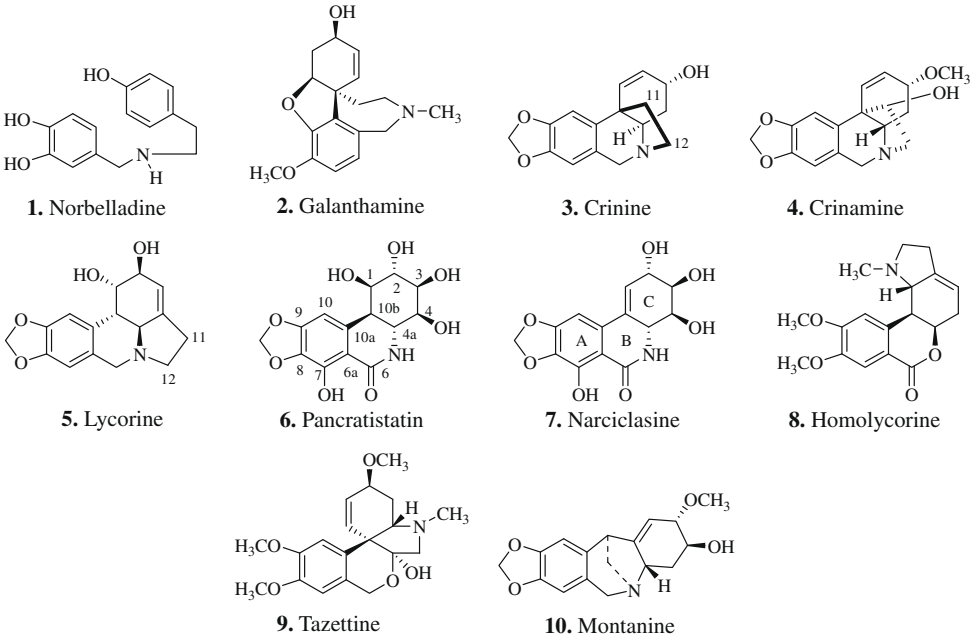
seco-Derivatives of the anticancer agent pancratistatin bearing the 2*S*,3*S*,4*S*,5*S* configuration were accessed via a novel, highly diastereoselective *anti*-aldol reaction. Structure–activity relationships reveal important insights into the *seco*-pancratistatin pharmacophore as a potent and selective inhibitor of human cytochrome P450 3A4 (CYP3A4), and highlight features of concern in advancing a potent, selective anticancer agent in the pancratistatin series.

The plant family Amaryllidaceae produces an array of structurally-diverse alkaloids arising biosynthetically from the common amino acid-derived precursor norbelladine **1** (Scheme 1).[1] Galanthamine **2**, crinine **3**, and lycorine **5** are representative of the three major structural types within the family although six other minor groups are known to occur, including homolycorine **8**, tazettine **9**, and montanine **10**.[1] The interesting biological properties exhibited by several alkaloids of the Amaryllidaceae has garnered wide interest in terms of the phytochemical, synthetic, semi-synthetic, and biological evaluation aspects of these compounds, areas in which we have been active for a number of years now.[2] In particular, the cell-line specific anticancer activity displayed by pancratistatin **6** and narciclasine **7**, as well as their challenging molecular structure has attracted sustained synthetic efforts over the past two decades.[3] Galanthamine **2** is the first representative of this group of alkaloids to receive approval as a scheduled drug in the treatment of Alzheimer's disease due to its ability to reversibly inhibit acetylcholinesterase.[1c] Amongst the other series within the Amaryllidaceae, crinane compounds (such as **3**) are known to inhibit protein synthesis and have antimalarial and antiproliferative activity.[4] Recent findings in our laboratories uncovered the selective apoptosis-initiating ability of α-bridged crinanes (such as **4**) in rat liver hepatoma (5123tc) but not in normal HEK293t cells, notably distinguishing them from inactive β-variants (such as **3**).[4f,g] Lycorine **5** is the most common alkaloid across the Amaryllidaceae and its broad spectrum of biological activities is well documented.[4d,e,5a–l] It has been shown to be a promising chemotherapeutic agent with antiproliferative action in a number of cancer cell lines.[4e] Lycorine has recently been identified as a selective[5k] initiator of apoptosis in human leukemia (Jurkat) cells and as a selective cytostatic agent in a mini-panel of cancer cell lines.[5l] The essential elements of this remarkable pharmacophore have been documented in two recent reports.[5k,l]

Following on the commercial success of galanthamine **2** and given the potent and selective anticancer activity of pancratistatin **6** and narciclasine **7**, it is widely held that an anticancer clinical candidate will emerge from the lycorane group. Pharmacophore minimization efforts by us and others have revealed several crucial elements of this promising anticancer pharmacophore; in particular, the stereodefined 2,3,4-trihydroxy functionalized ring C is essential for potent apoptosis-inducing activity.[2a–e] This was shown by us to occur selectively in cancer cells but not in normal cells and that the process was localized within mitochondria of cancerous cells.[6] Early activation of caspase-3 followed by flipping of phosphatidyl serine to the outer leaflet of the plasma membrane were diagnostic of the apoptotic mode of death initiated by pancratistatin.[6] It is also important to note recent studies that show that narciclasine disrupts organization of the actin skeleton in cancer cells at lower (30–90 nM) concentrations.[3s] Narciclasine has also been shown to increase survival in preclinical models of human glioblastoma multiforme and clearly has much potential.

* Corresponding author. Tel.: +1 905 525 9140×27393; fax: +1 905 522 2509.
E-mail address: jmcnult@mcmaster.ca (J. McNulty).

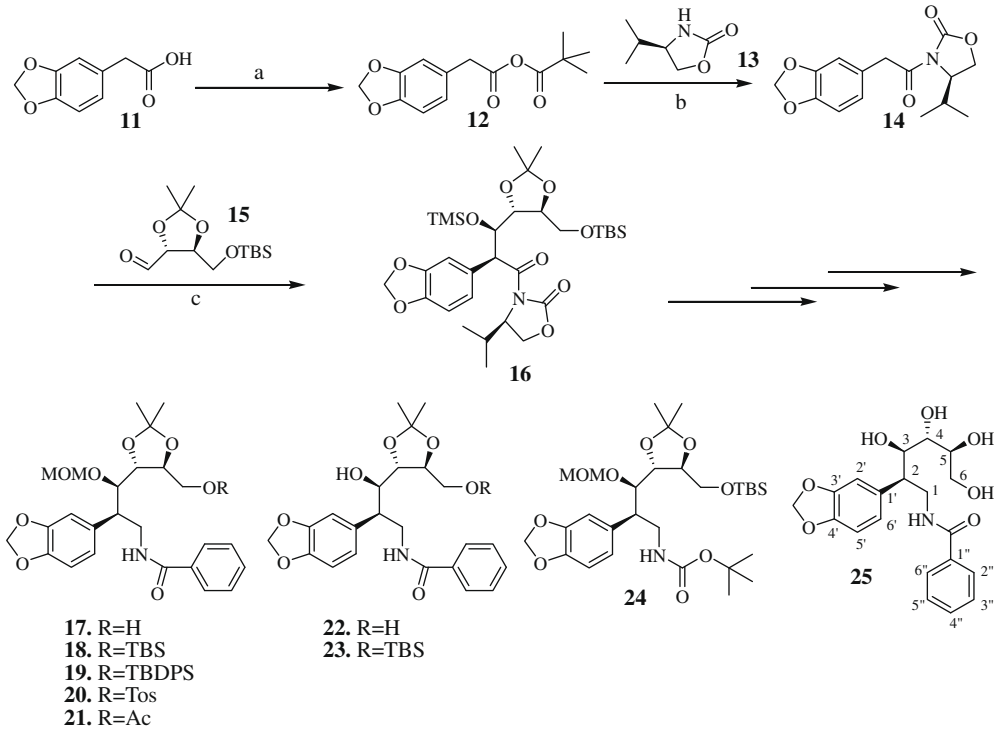
0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.01.157



Scheme 1. Structurally-diverse alkaloid representatives of the plant family Amaryllidaceae.

In view of the potential clinical development of an anticancer agent within the lycorane series,[3a–c] we recently documented for the first time the human cytochrome (CYP3A4) inhibitory activity of a compound library consisting of 26 amaryllidaceae alkaloids and derivatives.[8] Cytochromes P450 (CYP450) are heme-containing mono-oxygenase enzymes that are expressed primarily on smooth ER membranes of hepatocytes and by cells along the intestinal tract mucosal surface.[7a] They are involved in the detoxification of a wide variety of xenobiotics such as drugs and environmental toxins.[7b] The CYP3A subfamily comprises about 30% of the total liver cytochrome P450 enzyme pool in humans, and the isoenzyme CYP3A4 accounts for approximately 60% of drugs metabolized.[7b] In addition, an estimated 70% of CYP protein in the small intestinal epithelium is formed by this isoenzyme.[7c] Thus, evaluation of CYP3A4-drug interactions is critical to the identification of a selective clinical candidate. From our initial study[8] we documented that pancratistatin **6** exhibited low interaction with CYP3A4 while narciclasine **7** proved to be a potent inhibitor. In addition, we determined that lipophilic substitution at positions 1 and 2 in the lycorine series **5** resulted in the formation of potent CYP3A4 inhibitors one magnitude less active than the clinically used antifungal P450 inhibitor ketoconazole.[8] We also examined a mini-panel of conformationally flexible semi-synthetic *seco*-pancratistatin derivatives uncovering further structural information concerning CYP3A4 inhibitory activity.[9] The *seco*-analogs were prepared via a non-Evans' *anti*-selective aldol[10] reaction that gave *anti*-adduct **16** as the major diastereomer (95:5) in 95% isolated yield (Scheme 2, step c).[2f,g] Elaboration of adduct **16** (Scheme 2) led to the *seco*-pancratistatin target **25** which possesses all of the essential elements of the known anticancer pharmacophore, including the stereodefined 1,2,3,4-tetrahydroxy motif and the amide functionality, but in a conformationally mobile form.[2g,9] It was shown that *seco*-pancratistatin **25** exhibited no CYP3A4 inhibitory activity. In contrast, the *seco*-analogs **18** and **20** were found to be as potent as ketoconazole (K_i 0.03 and 0.07 μM, respectively) at the inhibition of CYP3A4.[9] This result justifies the utility of these *seco*-amaryllidaceae analogs as probes useful in highlighting CYP3A4 interactions. This study revealed lipophilic substitution at C3 as a key factor for potent CYP3A4 inhibition,[9] results consistent with our earlier observations with lycorine derivatives.[8] *Nonetheless, we highlight that the two series differ with respect to the absolute configuration at both C2 and C3.*

Herein we report an entry to the C2/C3 diastereomeric series of *seco*-pancratistatin analogs using a non-auxiliary directed approach and identify MOM benzamide **32** as a potent CYP3A4 inhibitor (K_i 0.03 μM), and overall provide a more comprehensive view of this important antioxidant pharmacophore. Esterification of (3,4-methylenedioxy)phenylacetic acid **11** with 2-bromopropane under basic conditions in acetonitrile gave isopropyl (3,4-methylenedioxy)phenylacetate **26** in 95% isolated yield (Scheme 3). The reaction of the lithium enolate of **26** with L-threose aldehyde **15** was found highly diastereoselective leading to the *anti*-adduct **27** as a single diastereomer in 90% yield (Scheme 3, step b).[11] Only a few reports exist involving the use of phenylacetic esters in aldol chemistry. This may be due to the modest diastereoselectivities observed through formation of mixtures of *E*- and *Z*-enolates.[12] Previous reports on nucleophilic addition to aldehyde **15** have explained observed selectivities through intrinsic diastereoselectivity in accord with the Felkin–Ahn model.[13] To the best of our knowledge, this work is the first document of an aldol between a phenylacetic ester and L-threose aldehyde **15**. Protection of the 3-hydroxy group in **27** as the MOM ether (Scheme 3, step c) followed by $LiAlH_4$ reduction of ester **28** gave alcohol **29** in 93% yield. The primary hydroxyl group in **29** was converted to the bromide **30** via nucleophilic bromination with NBS/triphenylphosphine/TEA, and underwent smooth displacement with sodium azide over 5 h at room temperature to give in 93% isolated yield azide **31**. Reduction of azide **31** over 10% palladium on carbon and subsequent benzoylation of the free amine secured MOM-benzamide **32** in near quantitative yield. In a similar fashion, carbamate **34** was obtained from azide **31** via the free amine by reaction with Boc-anhydride and TEA. Double recrystallization of **34** from ethyl acetate provided a sample for single crystal X-ray analysis (Fig. 1) confirming it to be the 2*S*,3*S* stereoisomer, and providing unequivocal proof of the initial *anti* aldol. Desilylation of MOM-benzamide **32** with TBAF proceeded smoothly to the hydroxybenzamide **35** which was then functionalized as the *O*-tosylate **36**. Straightforward global deprotection of **32** with 2 M HCl led to



Scheme 2. Synthesis of *seco*-pancratistatin analogs via Evans' catalytic *anti*-aldol reaction as key step. Reagents and conditions: (a) PivCl, TEA, DEE, −78 °C to rt, 2 h; (b) LiHMDS, THF, −78 °C to rt, 6 h, 84%; and (c) $MgCl_2$, TEA, TMSCl, EtOAc, rt, 12 h, 95%.

the tetrahydroxybenzamide **33** (89%), yielding the targeted C2/C3 diastereomeric variant of *seco*-pancratistatin **25** and analogs shown.

The mini-library comprising functionalized truncated compounds **27**–**36** (Scheme 3) was screened for CYP3A4 activity as previously reported (see Supplementary data), utilizing ketoconazole as control (Table 1).[8,9] The inhibitory activity of MOM-benzamide **32** (K_i 0.03 μM) is immediately striking, seen in Table 1 to be as potent as ketoconazole. Compounds **27**–**31** were all inactive as was *seco*-pancratistatin **33**. A pronounced ~60-fold reduction in activity is observed in going from MOM-benzamide **32** to desilylated hydroxy analog **35** (K_i 1.78 μM). Inhibition is sustained with the introduction of an *O*-tosylate group at C6 as in **36** (K_i 0.07 μM) while replacement of the benzamide moiety in **32** with a *t*-butyl carbamate resulted in a ~10-fold decrease in activity as evident for **34** (K_i 0.24 μM). The overall SAR data is consistent with our previous observations in both the lycorane[8] and *seco*-pancratistatin[9] series and provides for further insights into essential pharmacological elements of the potent CYP3A4 inhibitors **32** and **36**.

It is apparent that the 1-benzamide functionality is essential as compounds **27**–**31** were inactive and since there is a ten fold difference in activity between MOM-1-benzamide **32** and MOM-1-carbamate **34**. This suggests that the C1 part of the molecule must occupy a fairly bulky, polar pocket within the enzyme active site with the amide entity possibly functioning as an H-bond acceptor.

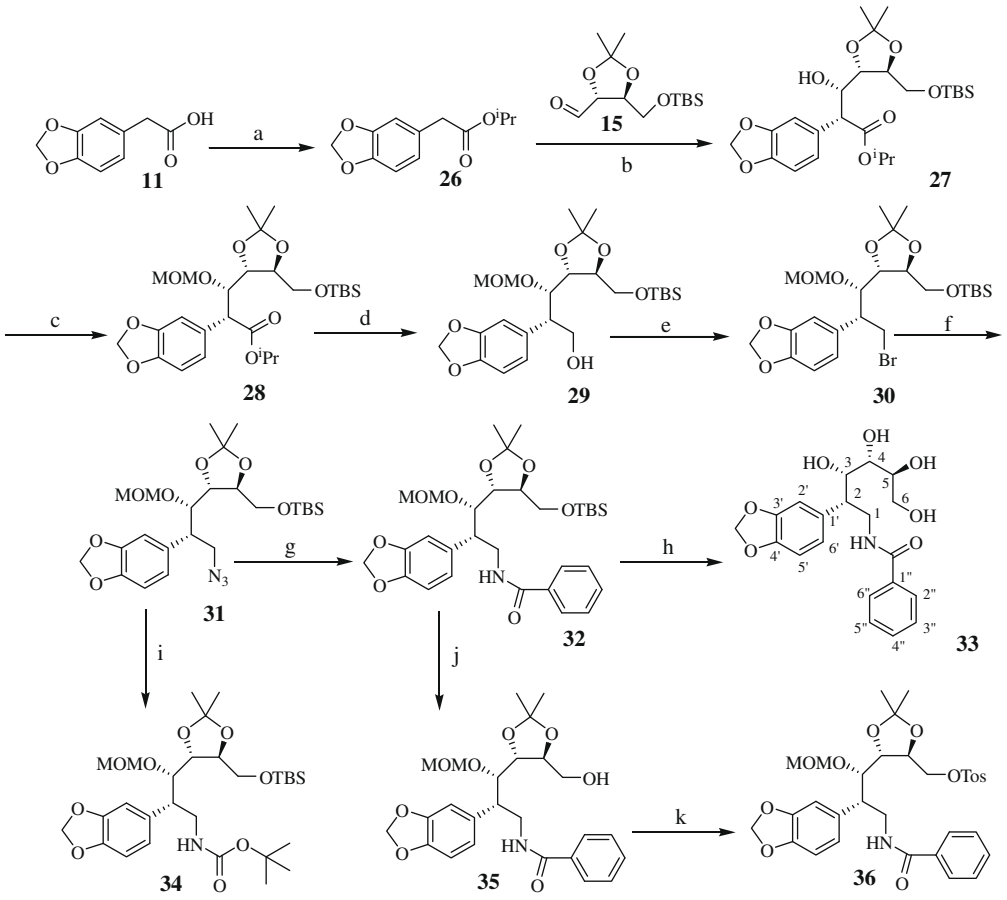
Substitution at C6 is seen to be quite sensitive, for example comparing **32** versus **35** (Table 1) pointing to a moderately sized lipophilic binding site within the enzyme. Again, these results are fully in accordance with K_i values recorded for **17** (1.55 μM) and **18** (0.03 μM)[9] (Scheme 2), as well as the pronounced CYP3A4 inhibitory effects of TBS-substituted derivatives of lycorine **5**.[8] Overall, the introduction of functional groups at C6 other than TBS had varying effects on inhibitory activity.

The bulky 6-TBDPS group (**19**, Scheme 2) proved somewhat detrimental to CYP3A4 inhibition (K_i 0.58 μM) while introduction of a small, polar group such as acetate **21** results in further loss of activity (K_i 1.01 μM). While the OTBS-substituent at C6 appears optimal, inhibition is maintained with the introduction of an *O*-tosylate group at C6 as seen in both **36** (K_i 0.07 μM) and **20**.

Cleavage of both 3-MOM and 6-TBS groups resulted in complete lack of activity as shown for 3,6-diol **22** (Scheme 2) while a further loss of the 3,4-isopropylidene group also produced inactive tetrahydroxybenzamide **25**.[9] These results are in accord with our previous findings wherein a small H-bond acceptor at C3 was found optimal. The fact that **25** and **33** were both inactive again highlights the requirement for lipophilic substitution around C3/C4/C5 in the *seco*-pancratistatin series. The isopropylidene group may also serve as a conformational anchor within a more rigid portion of the enzyme.

While all of the above data show a consistent pattern of CYP3A4 activity, perhaps the most striking result is the total lack of relation of this activity to either the 2*S*,3*S* (Scheme 3) or 2*R*,3*R* (Scheme 2)[9] diasteromeric series of *seco*-pancratistatin derivatives. Our attention was first drawn to this discrepancy in contrasting the potent CYP3A4 inhibitory lycorines[8] with potent 2*R*,3*R* seco-analogs,[9] derivatives that display opposite absolute configuration at C2 and C3. The present results fully confirm the generality of this remarkable effect. For example *seco*-derivatives **32** and **18** both exhibited a K_i of 0.03 μM, as potent as the clinical antifungal P450 inhibitor ketoconazole. Likewise, the next potent derivatives in both series are the C6 tosyl derivatives **36** and **20**, that both exhibited K_i values of 0.07 μM. Reversal of the stereochemistry at C2 and C3 has no apparent effect on CYP3A4 inhibition, nonetheless we have shown that C3 must contain a small lipophilic H-bond acceptor. The conformational mobility in both sets of potent *seco*-pancratistatin analog may allow either series to occupy a less rigid portion of the enzyme active site in the C2/C3 region.

In conclusion, we report a concise, efficient strategy towards the synthesis of fully functionalized *seco*-pancratistatin analogs **32**–**36** bearing the 2*S*,3*S*,4*S*,5*S* absolute configuration. Rapid entry to this



Scheme 3. Synthesis of *seco*-pancratistatin analogs employing as key step an aldol of the lithium enolate of isopropyl (3,4-methylenedioxyphenyl) acetate. Reagents and conditions: (a) $CH_3CHBrCH_3$, K_2CO_3, MeCN, reflux, 6 h, 95%; (b) LiHMDS, THF, −78 °C to rt, 2 h, 90%; (c) DIPEA, MOMCl, DCM, 0 °C to rt, 10 h, 96%; (d) $LiAlH_4$, THF, 0 °C to rt, 3 h, 93%; (e) NBS, PPh_3, TEA, DCM, 0 °C to rt, 5 h, 88%; (f) NaN_3, DMF, rt, 5 h, 93%; (g) (i) 10% Pd/C, H_2, THF, rt, 3 h; (ii) BzCl, TEA, DCM, rt, 2 h, 98%; (h) 2 M HCl, THF, rt, 2 h, 89%; (i) (i) 10% Pd/C, H_2, THF, rt, 3 h; (ii) Boc_2O, TEA, DCM, rt, 2 h, 98%; (j) TBAF, THF, rt, 1 h, 97%; and (k) TosCl, py, DCM, rt, 5 h, 98%.

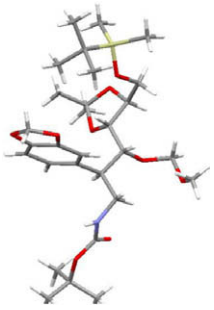


Figure 1. X-ray structure of carbamate **34**.

Table 1
Inhibitory activity against the biotransformation of 7-benzyloxyquinoline by cDNA-expressed human CYP3A4

Compound	K_i (μM)	pK_i (M)[a]
27	na	—
29	na	—
31	na	—
32	0.03	7.54 (±0.01)
33	na	—
34	0.24	6.62 (±0.04)
35	1.78	5.75 (±0.02)
36	0.07	7.16 (±0.05)
Ketoconazole	0.03	7.48 (±0.02)

[a] Values are means of three experiments, standard deviation is given in parentheses (na = not active at 10 μM).

series was realized via a highly diastereoselective lithium enolate mediated aldol reaction of phenylacetate **26** with L-threose aldehyde **15**. The novel 2*S*,3*S*-analogs are in contrast to the corresponding 2*R*,3*R*-variants **17**–**25** previously reported. A more general and detailed SAR study has evolved, in conjunction with our previous studies[8,9] allowing for the following conclusions to be made for potent CYP3A4 activity. (i) A small H-bond acceptor region at C3 (C1 in the lycorane series[8]) leads to significant interaction with CYP3A4. The strongest cytochrome interaction was seen for the flexible C3 *O*-MOM group. (ii) A lipophilic substituent at C6 is required for potent activity. (iii) Bulky lipophilic substitution at C4 (C2 in the lycorane series[8]) enhances inhibition, indicative of a large hydrophobic binding pocket in the enzyme active site. The overall effects of (i), (ii), and (iii) also appear additive in that the most potent cytochrome inhibitors have both a small, flexible H-bond acceptor at C3 and lipophilic substituents at C4 and C6. (iv) There appears no relation of the CYP3A4 inhibitory activity to the absolute stereochemistry at C2 and C3 in these conformationally mobile *seco*-diastereomers. These results clearly point to potential problems with lipophilic functionalization, particularly at C3, corresponding to the C1 position in the natural pancratistatin series. This area was also highlighted as critical wherein we showed narciclasine **7** to be a potent inhibitor, while pancratistatin **6** proved inactive to CYP3A4. It now appears likely that the polar C1 hydroxyl group present in pancratistatin prevents its interaction with

this critical metabolizing enzyme and thus contributes significantly to the selective anticancer versus P450 interactive activity observed.

All of the *seco*-analogs **17**–**25** and **31**–**36** reported in Schemes 2 and 3 were found to be devoid of anticancer activity (MCF-7) at 10 μM concentration, in sharp contrast to pancratistatin and narciclasine positive controls. These results are in complete agreement with prior work from various laboratories,[2,3] showing that a fully functionalized, 2,3,4-triol-containing phenanthridone is required for cystostatic activity.

Lastly, we have identified two potent derivatives **18** and **32** that exhibit CYP3A4 inhibitory activity at the nanomolar level, as well as two slightly less potent derivatives **20** and **36**. This activity is similar to the clinical antifungal agent ketoconazole. Extension of these leads towards the synthesis of novel, selective antifungal agents are in progress in our laboratories.

Acknowledgments

We thank NSERC and McMaster University for financial support of this work. We are grateful to Dr. D. Hughes for obtaining high field NMR data and Dr. J. F. Britten for obtaining the crystallographic data.

Supplementary data

Supplementary data (CCDC file 654288 contains the supplementary crystallographic data for **34**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.01.157.

References and notes

1. Bastida, J.; Lavilla, R.; Viladomat, F.. In *The Alkaloids*; Cordell, G. A., Ed.; Elsevier: Amsterdam, 2006; Vol. 63, pp 87–179; (b) Jin, Z. *Nat. Prod. Rep.* **2007**, *24*, 886; (c) Houghton, P. J.; Ren, Y.; Howes, M. J. *Nat. Prod. Rep.* **2006**, *23*, 181.
2. (a) McNulty, J.; Mo, R. *J. Chem. Soc., Chem. Commun.* **1998**, 933; (b) McNulty, J.; Mao, J.; Gibe, R.; Mo, R.; Wolf, S.; Pettit, G. R.; Herald, D. L.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 169; (c) Hudlicky, T.; Rinner, U.; Gonzales, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726; (d) Rinner, U.; Hillebrenner, H. L.; Adams, D. R.; Hudlicky, T.; Pettit, G. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2911; (e) McNulty, J.; Larichev, V.; Pandey, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315; (f) McNulty, J.; Nair, J. J.; Sliwinski, M.; Harrington, L. E.; Pandey, S. *Eur. J. Org. Chem.* **2007**, 5669; (g) McNulty, J.; Nair, J. J.; Griffin, C.; Pandey, S. *J. Nat. Prod.* **2008**, *71*, 357; (h) Pettit, G. R.; Pettit, G. R., III; Backhaus, R. A.; Boyd, M. R.; Meerow, A. W. *J. Nat. Prod.* **1993**, *56*, 1682.
3. (a) Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982; (b) Chapleur, Y.; Chretien, F.; Ibn Ahmed, S.; Khaldi, M. *Curr. Org. Synth.* **2006**, *3*, 169; (c) Dumont, P.; Ingrassia, L.; Rouzeau, S.; Ribacour, F.; Thomas, S.; Roland, I.; Darro, F.; Lefranc, F.; Kiss, R. *Neoplasia* **2007**, *9*, 766; (d) Pettit, G. R.; Melody, N. *J. Nat. Prod.* **2005**, *68*, 207; (e) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365; (f) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829; (g) Tian, X. R.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643; (h) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143; (i) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289; (j) Hudlicky, T.; Tian, X. R.; Konigsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752; (k) Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153; (l) Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509; (m) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341; (n) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624; (o) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343; (p) Ko, H.; Kim, E.; Park, J. E.; Kim, D.; Kim, S. *J. Org. Chem.* **2004**, *69*, 112; (q) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583; (r) Collins, J.; Drouin, M.; Sun, X.; Rinner, U.; Hudlicky, T. *Org. Lett.* **2008**, *10*, 361; (s) Ingrassia, L.; Lefranc, F.; Dewelle, J.; Pottier, L.; Mathieu, V.; Spiegl-Kreinecker, S.; Sauvage, S.; El Yazidi, M.; Dehoux, M.; Berger, W.; van Quaquebeke, E.; Kiss, R. *J. Med. Chem.* **2009**, *52*, 1100; (t) Manpadi, M.; Kireev, A. S.; Magedov, I. V.; Altig, J.; Tongwa, P.; Antipin, M. Y.; Evidente, A.; van Otterlo, W. A. L.; Kornienko, A. *J. Org. Chem.* **2009**, *74*, 7122.
4. (a) Tram, N. T. M.; Titorenkova, T. V.; Bankova, V. S.; Handjieva, N. V.; Popov, S. S. *Fitoterapia* **2002**, *73*, 183; (b) Nair, J. J.; Campbell, W. E.; Gammon, D. W.; Albrecht, C. F.; Viladomat, F.; Codina, C.; Bastida, J. *Phytochemistry* **1998**, *49*, 2539; (c) Hohmann, J.; Forgo, P.; Molnar, J.; Wolfard, K.; Molnar, A.; Thalhammer, T.; Mathe, I.; Sharples, D. *Planta Medica* **2002**, *68*, 454; (d) Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochim. Biophys. Acta* **1976**, *425*, 342; (e) Likhitwitayawuid, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 1331; (f) McNulty, J.; Nair, J. J.; Codina, C.; Bastida, J.; Pandey, S.; Gerasimoff, J.; Griffin, C. *Phytochemistry* **2007**, *68*, 1068; (g) McNulty, J.; Nair, J. J.; Bastida, J.; Pandey, S.; Griffin, C. *Nat. Prod. Commun.* **2009**, *4*, 483.
5. (a) Hwang, Y. C.; Chu, J. J. H.; Yang, P. L.; Chen, W.; Yates, M. V. *Antiviral Res.* **2008**, *77*, 232; (b) Deng, L.; Dai, P.; Ciro, A.; Smee, D. F.; Djaballah, H.; Shuman, S. *J. Virol.* **2007**, *81*, 13392; (c) Li, R.; Tan, X. *Antiviral Res.* **2005**, *67*, 18; (d) Del Giudice, L.; Massardo, D. R.; Pontieri, P.; Wolf, K. *Gene* **2005**, *354*, 19; (e) Mackey, Z. B.; Baca, A. M.; Mallari, J. P.; Apsel, B.; Shelat, A.; Hansell, E. J.; Chiang, P. K.; Wolff, B.; Guy, K. R.; Williams, J.; McKerrow, J. H. *Chem. Biol. Drug Des.* **2006**, *67*, 355; (f) Citoglu, G.; Tanker, M.; Gamusel, B. *Phytotherapy Res.* **1998**, *12*, 205; (g) Evidente, A.; Arrigoni, O.; Luso, R.; Calabrese, G.; Randazzo, G. *Phytochemistry* **1986**, *25*, 2739; (h) Arrigoni, O.; Arrigoni Liso, R.; Calabrese, G. *Nature* **1975**, *256*, 513; (i) Lopez, S.; Bastida, J.; Viladomat, F.; Codina, C. *Life Sci.* **2002**, *71*, 2521; (j) De Leo, P.; Dalessandro, G.; De Santis, A.; Arrigoni, O. *Plant Cell Physiol.* **1973**, *14*, 481; (k) McNulty, J.; Nair, J. J.; Bastida, J.; Pandey, S.; Griffin, C. *Phytochemistry* **2009**, *70*, 913; (l) Lamoral-Theys, D.; Andolfi, A.; Van Goietsenoven, G.; Cimmino, A.; Le Calve, B.; Wauthoz, N.; Megalizzi, V.; Gras, T.; Bruyere, C.; Dubois, J.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. *J. Med. Chem.* **2009**, *52*, 6244.
6. (a) Kekre, N.; Griffin, C.; McNulty, J.; Pandey, S. *Cancer Chemother. Pharmacol.* **2005**, *56*, 29; (b) McLachlan, A.; Kekre, N.; McNulty, J.; Pandey, S. *Apoptosis* **2005**, *10*, 619; (c) Lefranc, F.; Sauvage, S.; Van Goietsnoven, G.; Megalizzi, V.; Lamoral-Theys, D.; Debeir, O.; Spiegl-Kreinecker, S.; Berger, W.; Mathieu, V.; Decaestecker, C.; Kiss, R. *Mol. Cancer Ther.* **2009**, *8*, 1739.
7. (a) Nelson, D. R.; Zeldin, D. C.; Hoffman, S. M. G.; Maltais, L. J.; Wain, H. W.; Nebert, D. W. *Pharmacogenetics* **2004**, *14*, 1; (b) de Graaf, C.; Vermeulen, N. P. E.; Feenstra, K. A. *J. Med. Chem.* **2005**, *48*, 2725; (c) Rendic, S.; DiCarlo, F. J. *Drug Metab. Rev.* **1997**, *29*, 413.
8. McNulty, J.; Nair, J. J.; Singh, M.; Crankshaw, D. J.; Holloway, A. C.; Bastida, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3233.
9. McNulty, J.; Nair, J. J.; Singh, M.; Crankshaw, D. J.; Holloway, A. C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5607.
10. Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.
11. We subsequently determined this reaction to be of broad applicability to various aldehydes and will report these general studies elsewhere. McNulty, J.; Nair, J. J., in preparation.
12. (a) van Aardt, T. J.; van Rensburg, H.; Ferreira, D. *Tetrahedron* **1999**, *55*, 11773; (b) Canceill, J.; Basselier, J.-J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, 1024; (c) Tanaka, F.; Node, M.; Tanaka, K.; Mizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc.* **1995**, *117*, 12159; (d) Solladie-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343; (e) Corset, J.; Froment, F.; Lautie, M.-F.; Ratovelomanana, N.; Seyden-Penne, J.; Strzalko, T.; Roux-Schmitt, M.-C. *J. Am. Chem. Soc.* **1993**, *115*, 1684; (f) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 2336; (g) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873; (h) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087.
13. Chattopadhyay, A.; Dhotare, B. *Tetrahedron: Asymmetry* **1998**, *9*, 2715; (b) Majewski, M.; Shao, J.; Nelson, K.; Nowak, P.; Irvine, N. M. *Tetrahedron Lett.* **1998**, *39*, 6787; (c) Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 7045; (d) Mukaiyama, T.; Suzuki, K.; Yomada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265; (e) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.