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# Optimization of small molecule agonists of the thrombopoietin (Tpo) receptor derived from a benzo[*a*]carbazole hit scaffold

Thomas H. Marsilje *, Phil B. Alper, Wenshuo Lu, Daniel Mutnick, Pierre-Yves Michellys, Yun He, Donald S. Karanewsky, Donald Chow, Andrea Gerken, Jianmin Lao, Min-Ju Kim, H. Martin Seidel, Shin-Shay Tian

*Genomics Institute of the Novartis Research Foundation (GNF), San Diego, CA 92121, USA*

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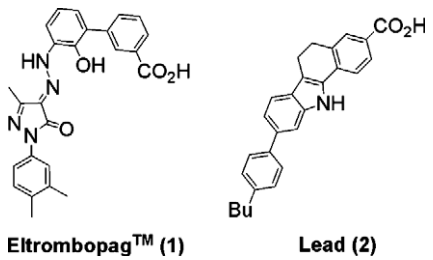
ABSTRACT

The lead optimization of a novel series of benzo[*a*]carbazole-based small molecule agonists of the thrombopoietin (Tpo) receptor is reported. The chemical instability of the dihydro-benzo[*a*]carbazole lead **2** was successfully addressed in the design and evaluation of compounds which also demonstrated improved potency compared to **2**. Members of the scaffold have been identified which are full agonists that demonstrate cellular functional potency <50 nM. Analog **21** demonstrates equivalent efficacy in the human megakaryocyte differentiation (CFU-mega) assay compared to Eltrombopag™.



The preceding publication in this journal describes our initial identification of a structurally novel series of human Tpo receptor agonists based upon the benzo[*a*]carbazole ring system.[1] Figure 1 shows the known[2–5] TpoR agonist Eltrombopag™ (**1**) as well as a representative lead structure from our initial SAR exploration (**2**). As previously discussed,[1] the dihydro-benzo[*a*]carbazole scaffold suffers from chemical instability via spontaneous oxidation of its ethylene bridge yielding the fully aromatic benzo[*a*]carbazole ring system. We wanted to avoid the fully aromatic system for two reasons: (a) the possibility of oxidation of the 5,6-double bond in vivo potentially generating a reactive species and (b) the flat fully aromatic nature of this molecule making intercalation into DNA an undesired possibility. Additionally, the chemical instability issue of the ethylene bridge would preclude the pharmaceutical development of this TpoR agonist scaffold. Thus, a focus of our optimization of this lead scaffold was to identify strategies to address the chemical instability of the ethylene bridge while retaining or improving functional potency in the agonism of the TpoR. Simultaneously, we were also interested in identifying structural modifications to reduce the high lipophilicity of the lead scaffold ideally through the same bridge modifications used to address the lead's chemical instability. A series of ethylene bridge modifications are shown in Table 1.

Contracting the ethylene bridge of **2** to one carbon (**3**) results in a compound with only slightly reduced potency (160 nM) which retains almost full efficacy (91%). We were very encouraged by these results since compound **3** was significantly more chemically stable than compound **2**. For example, when heated in DMSO solution, **3** appeared to be completely stable by LC–MS analysis. In contrast, **2** degrades to oxidation by-products under the same conditions. Replacement of the carboxylic acid at $R^4$ with a primary carboxamide slightly improves both potency (86 nM) and efficacy (118%). The non-essential requirement of a negatively charged group at the $R^4$ position for both potency and efficacy mirrors the SAR seen in our previous study.[1] Since the lead molecule's ethylene bridge had been contracted to a shorter methylene bridge,




**Eltrombopag™ (1)** **Lead (2)**

**Figure 1.** Eltrombopag™ (**1**) and lead structure (**2**).

* Corresponding author. Tel.: +1 858 332 4604; fax: +1 858 812 1648.
*E-mail address:* TMarsilje@gnf.org (T.H. Marsilje).

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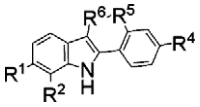
**Table 1**
In vitro human TpoR functional activity of alternate bridges[a]




| Compound[a] | $R^1$ | $R^2$ | $R^4$ | $R^5$ | $R^6$ | $EC_{50}$ (μM)[b] | % Efficacy[c] |
|---|---|---|---|---|---|---|---|
| **2** | 4′-*n*-Butylphenyl | H | $CO_2H$ | $CH_2$ | $CH_2$ | 0.111 | 141 |
| **3** | 4′-*n*-Butylphenyl | H | $CO_2H$ | Bond | $CH_2$ | 0.160 | 91 |
| **4** | 4′-*n*-Butylphenyl | H | $CONH_2$ | Bond | $CH_2$ | 0.086 | 118 |
| **5** | 4′-*n*-Butylphenyl | F | $CO_2H$ | Bond | $CH_2$ | 0.037 | 151 |
| **6** | 3′-Methyl-4′-fluorophenyl | F | $CO_2H$ | Bond | $CH_2$ | 0.026 | 144 |
| **7** | 3′-Methyl-4′-fluorophenyl | F | $CONH_2$ | Bond | $CH_2$ | 0.277 | 105 |
| **8** | 4′-*n*-Butylphenyl | F | $CO_2H$ | Bond | $C(CH_3)_2$ | 0.111 | 118 |
| **9**[d] | 4′-*n*-Butylphenyl | H | $CO_2H$ | $CH_2$–$CH_2$ | $CH_2$ | 0.332 | 71 |
| **10** | 4′-*n*-Butylphenyl | H | $CO_2H$ | $SO_2$ | $CH_2$ | 0.449 | 115 |
| **11** | 3′-Methyl-4′-fluorophenyl | F | $CONH_2$ | O | $CH_2$ | 1.43 | 83 |
| **12** | 3′-Methyl-4′-fluorophenyl | F | $CONH_2$ | $CH_2$ | $CO_2$ | >30 | 0 |
| Eltrombopag™ (**1**) | | | | | | 0.038 | 127 |

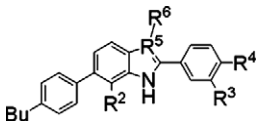
[a] All compounds demonstrated satisfactory LC–MS and $^1H$ NMR characterization.
[b] Ba/F3-hTpoR RGA.[6,7]
[c] Relative to 30 ng/mL TPO.
[d] Assay conducted with 1 mM Zn.[8]

the correct placement of the primary carboxamide for interaction with the TpoR was confirmed by synthesizing the other possible carboxamide regioisomers. This confirmed that the most potent and efficacious carboxamide regioisomer is analog **3** (other data not shown). The addition of a fluorine onto **3** at $R^2$ (**5**) further increases potency to 37 nM and increases efficacy to 151% relative to Tpo. Replacing the $R^1$ 4′-*n*-butylphenyl group of **5** with 4′-fluoro-3′-methylphenyl (**6**) results in a very potent (26 nM) and efficacious (144%) compound with reduced lipophilicity (*c*Log*P* = 6.9 for **6** vs. 8.3 for **5**), albeit the *c*Log*P* is still higher than desired in a drug-like molecule. Surprisingly, the carboxamide version of this compound (**7**) is significantly less potent albeit efficacious, indicating that the scaffold is less tolerant of changes to the $R^4$ portion of the molecule when a less lipophilic $R^1$ group is employed. Compound **8** incorporates a *gem*-dimethyl group in the methylene bridge which would fully stabilize the bis-benzylic bridge position as well as introduce a tetra-substituted center in the molecule. We envisioned that this tetra-substituted center would further prevent the possibility of undesired DNA intercalation of our very flat, mostly aromatic scaffold as well as discourage π-stacking based aggregation, improving physiochemical properties of the scaffold. We were pleased that the *gem*-dimethyl analog 8 retains full efficacy although its potency (111 nM) drops by 3× compared to **5**. Expanding the bridge to three carbons yielded (**9**) which also retains significant potency albeit with reduced efficacy (71%) in comparison to the equivalent shorter bridge linker analogs (**2**, **3**).[8] Taken together, these data indicate the tolerance of the TpoR for different bridge linker lengths in this scaffold in terms of potency and partially in terms of efficacy. Analogs **10**–**12** introduce polar functionality into the linker bridge in an attempt to lower the lipophilicity of the scaffold. Introducing a sulfone for $R^5$ (**10**) loses fourfold in potency in comparison to **2**. Introducing an oxygen for $R^5$ (**11**) results in a drop in potency to the low micromolar range with 83% efficacy. Introducing an ester for $R^6$ (**12**) results in a complete loss of activity. In addition to the SAR described in Table 1, additional SAR exploration on the 6-position of the indole ring system ($R^1$ in Table 1) was performed in an attempt to decrease the scaffold's high lipophilicity. The $R^1$ position was chosen for this SAR focus since preliminary SAR[1] indicated that this portion of the scaffold had the most steric room for modification. In general, potency correlated very well with the lipophilicity of $R^1$. In addition to the lipophilic substituents shown for $R^1$ in Table 1, only similar highly hydrophobic groups showed high potency. A small number of less lipophilic aromatic heterocyclic replacements for the benzenoid rings in **2** were attempted based upon overlapping the structures of **1** and **2**. These attempts generated compounds of significantly reduced activity. Ether and aniline substituents on the distal benzene ring ($R^1$ in Table 1) reduced *c*Log*P* slightly and were partially tolerated albeit with reduced activity (data not shown).

In addition to modifying the unstable ethylene bridge linker of **2**, we also investigated analogs in which the bridge is completely removed, i.e., 2-phenyl indoles and 2-phenyl benzimidazoles (Table 2). When the bridge is removed from **5** to generate the 2-phenyl indole **13**, this causes only a 3× loss in potency with retention of full efficacy. The 2-phenyl indole scaffold's potency is increased to ca. 50 nM by the reintroduction of a phenolic oxygen in the $R^3$ position (**15**). Adding substituents to the $R^6$ position ( **16–18**), causes a drop in activity correlated to an increase of the steric bulk of $R^6$. Two possible explanations for this SAR trend are: (1) the TpoR prefers a coplanar orientation of the indole and phenyl ring systems or (2) there is a steric clash with the TpoR in the analogs with large $R^6$ substituents. The former explanation parallels a recent SAR analysis of pyrimidine benzamide-based TpoR agonsts.[9] The benzimidazole analog **19** has a potency reduced to the micromolar range. Interestingly, the benzimidazole salicylate **20** regains ca. 7× potency compared to **19**, indicating a more pronounced dependence on the salicylate moiety for potency in the benzimidazole sub-series than in the 2-phenyl indole sub-series.

Since it had proven difficult to decrease the scaffold's lipophilicity by introducing hydrophilic functional groups onto the indole 6-position ($R^1$ in Table 1, data not shown), in addition to bridge modifications, we also attempted to decrease the *c*Log*P* of this series by introducing hydrophilic substituents in place of the carboxylic acid in analog **5** ($R^4$ position, Table 3). Replacing the carboxylic acid in **5** with an acetamido group (**21**) resulted in an equipotent compound which also retained full efficacy. Previous SAR had indicated that a negatively charged group was not required for receptor activation but it is interesting that the TpoR also tolerates displacement of the carbonyl away from the aromatic ring. Replacing the acetamido group with methanesulfonamido (**22**), ureido (**23**), and hydroxyacetamido (**24**) groups is partially tolerated but

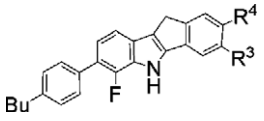
**Table 2**
In vitro human TpoR functional activity of unbridged analogs[a]




| Compound[a] | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | $EC_{50}$ (μM) [b] | % Efficacy[c] |
|---|---|---|---|---|---|---|---|
| **13** | F | H | $CO_2H$ | C | H | 0.117 | 112 |
| **14** | F | H | $CONH_2$ | C | H | 0.160 | 81 |
| **15** | F | OH | $CO_2H$ | C | H | 0.051 | 141 |
| **16** | F | OH | $CO_2H$ | C | $CH_3$ | 0.116 | 119 |
| **17** | F | OH | $CO_2H$ | C | $CH_2CH_3$ | 0.228 | 97 |
| **18** | F | OH | $CO_2H$ | C | $CH(CH_3)_2$ | >1 | 70 |
| **19** | H | H | $CO_2H$ | N | — | 1.26 | 83 |
| **20** | H | OH | $CO_2H$ | N | — | 0.179 | 121 |
| Eltrombopag™ (**1**) | | | | | | 0.038 | 127 |

[a] All compounds demonstrated satisfactory LC–MS and $^1H$ NMR characterization.
[b] Ba/F3-hTpoR RGA.[6,7]
[c] Relative to 30 ng/mL TPO.

**Table 3**
In vitro human TpoR activity of alternate head groups[a]




| Compound[a] | $R^3$ | $R^4$ | TpoR $EC_{50}$ (μM)[b] | % Efficacy[c] |
|---|---|---|---|---|
| **5** | H | $CO_2H$ | 0.037 | 151 |
| **21** | H | NHAc | 0.025 | 117 |
| **22**[d] | H | NHMs | 0.166 | 95 |
| **23**[d] | H | $NHCONH_2$ | 0.124 | 128 |
| **24**[d] | H | $NHCOCH_2OH$ | 0.087 | 98 |
| **25** | H | $NHCOCO_2H$ | 0.021 | 110 |
| **26**[d] | $NH_2$ | $CO_2H$ | 0.341 | 70 |
| **27** | NHAc | $CO_2H$ | 0.376 | 90 |

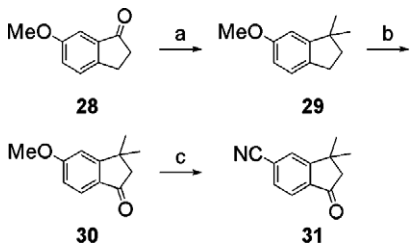
[a] All compounds demonstrated satisfactory LC–MS and $^1H$ NMR characterization.
[b] Ba/F3-hTpoR RGA.[6,7]
[c] Relative to 30 ng/mL TPO. NA, not applicable.
[d] Assay conducted with 1 mM Zn.[8]

causes a potency loss of 3–7×. In contrast, the oxalyl amide (**25**) is as active as the acetamido group (**21**) and it successfully reduces the *c*Log*P* from 7.6 (**21**) to 6.3 (**25**), albeit the *c*Log*P* is still higher than desired in a drug-like molecule. Finally, the anthranilic acid (**26**) along with its acetylated derivative (**27**) are both ca. 10× less potent than **5**. A representative sample of scaffold analogs were tested in the human CFU-mega assay.[7] Compound **21** was the most potent analog identified and was found to have full efficacy relative to Tpo with an $EC_{50}$ of ca. 300 nM, equivalent to the activity of the clinically efficacious Eltrombopag™.

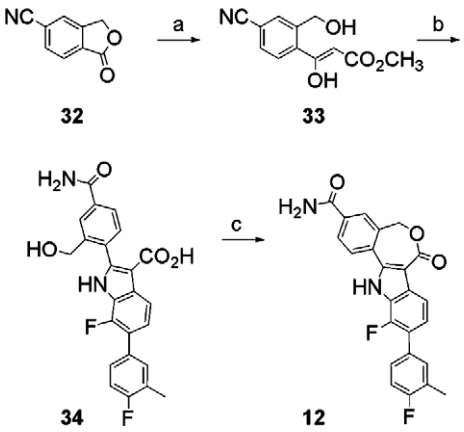
With the exception of **12**, the chemistry used to assemble the compounds in Table 1 is a Fisher indole synthesis reaction between the appropriate ketone and hydrazine in acetic acid at 100 °C overnight promoted by $ZnCl_2$.[10] In the cases where $R^4$ is a carboxylic acid, the corresponding ester was used for the Fisher indole formation and subsequently hydrolyzed with LiOH to generate the final carboxylic acid product. Likewise, in the cases where $R^4$ is an amide, the corresponding nitrile was used for the Fisher indole formation and subsequently hydrolyzed with LiOH to an amide in a final step. With the exception of the *gem*-dimethyl analog **8**, all of the required ketone and hydrazine synthetic fragments were either known in the literature or synthesized via standard synthetic manipulation of known literature intermediates.[10] The chemistry to generate the *gem*-dimethyl analog **8** required the synthesis of the requisite *gem*-dimethyl ketone **31** which is shown in Scheme 1. Commercially available 6-methoxy-indanone (**28**) was reacted with titanium tetrachloride and dimethyl zinc to convert the ketone functionality into the corresponding *gem*-dimethyl, generating intermediate **29**. This intermediate then underwent benzylic oxidation with chromium trioxide, generating the *gem*-dimethyl ketone intermediate **30**. Attempts to convert the methyl ether of 30 to the corresponding phenol using $BBr_3$ were unsuccessful. Instead, the phenol was produced *via* high temperature microwave irradiation of ether **30** in the presence of benzenethiol. The phenol was then converted into the penultimate nitrile ketone intermediate **31** via conversion first to a triflate intermediate followed by reaction with zinc cyanide under palladium catalyzed conditions.

The chemistry used to generate analog **12** is shown in Scheme 2. A base promoted condensation between 5-cyanophtalide (**32**) and diethyl malonate provided **33**. Intermediate **33** then reacted smoothly with 2-fluoro-3-(4′-fluoro-3′-methylphenyl)hydrazine hydrochloride in ethanol without added catalyst followed by hydrolysis with sodium hydroxide to afford **34**. Finally, treatment with HCl in dioxane at 100 °C for 5 min closed the lactone ring to provide the final product **12**.

In the case of analogs **13**–**18** (Table 2), the Fisher reaction was again employed to form the indole ring system.[11] The 4-*n*-butylphenyl moiety could either be introduced as a preexisting moiety on the hydrazine coupling partner in the Fisher reaction or alterna-




**Scheme 1.** Reagents and conditions: (a) titanium tetrachloride (2 equiv), dimethyl zinc (6 equiv), anhyd $CH_2Cl_2$/toluene, −40 °C to rt, 3 h; (b) chromium trioxide (2.3 equiv), 2:1 AcOH/$H_2O$, 0 °C to rt, 3 h; (c) i—benzenethiol (1 equiv), $K_2CO_3$ (0.1 equiv), NMP, 220 °C (microwave), 30 min, ii—triethylamine (3 equiv), *N*-phenyltrifluoromethanesulfonimide (1.1 equiv), anhyd $CH_2Cl_2$, −78 °C to rt, 12 h, iii—$ZnCN_2$ (2 equiv), palladium bis(tri-*tert*-butyl phosphine) (5 mol%), 2:1 THF/NMP, 120 °C, 3 h.



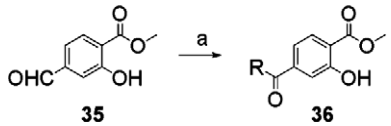
**Scheme 2.** Reagents and conditions: (a) diethyl malonate (1.5 equiv), NaOMe (3 equiv), MeOH, reflux, 5.5 h; (b) (i) (2,4′-difluoro-3′-methylbiphenyl-3-yl)-hydrazine hydrochloride (0.8 equiv), EtOH, 160 °C, 10 min, (ii) excess NaOH, 80 °C, 15 min; (c) EtOH/4 M HCl in dioxane (1:1), 100 °C, 5 min.

tively it could be installed after the Fisher reaction *via* a Suzuki reaction on the corresponding 6-halo synthetic intermediate. All of the precursor ketones were known in the literature or commercially available except the ketones required for **16–18** that were made as shown in Scheme 3. The known[12] aldehyde **35** was treated with **2** equivalents of the requisite Grignard reagent in THF and then oxidized to the ketone **36** using PDC.

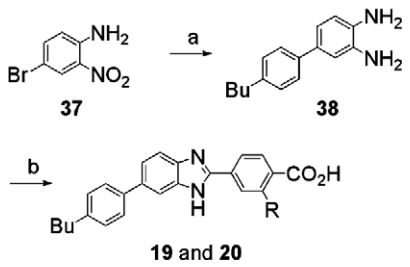
The chemistry to generate analog **20** is shown in Scheme 4. The bromide **37** was coupled with *n*-butylphenyl boronic acid under Suzuki conditions, followed by hydrogenation to afford the diamine **38**. This diamine was then oxidatively coupled with the appropriate aldehyde ester followed by ester saponification to afford the carboxylic acid analogs **19** and **20**.

In the case of analogs **26** and **27**, the requisite ketone for the Fisher reaction was prepared as shown in Scheme 5. The known[13] ketone **39** was elaborated to the styrene **40** using Suzuki chemistry and then oxidized to carboxylic acid **41** with $RuO_4$.

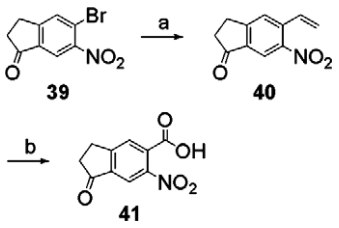
In conclusion, we designed and evaluated a series of TpoR agonists derived from a lead dihydro-benzo[*a*]carbazole scaffold which had been deemed unsuitable for pharmaceutical development due to inherent chemical instability.[1] The instability of the lead **2** was successfully addressed by compounds which also demonstrated improved potency compared to **2**. Members of the scaffold are full agonists of the human TpoR that demonstrate functional cellular potency <50 nM with analog **21** having equivalent activity in the primary human CFU-mega assay compared to the clinically efficacious Eltrombopag™. An examination of representative lead compounds in a cross-selectivity screen against >50 other receptors showed $IC_{50} > 1$ μM for all of the receptors evaluated, indicating that the observed TpoR activity is not simply due to non-specific hydrophobic binding or aggregation which is a concern for highly lipophilic lead structures. Clear SAR trends also support specific ligand interactions with a binding pocket in the human Tpo receptor. Although we were able to successfully identify molecules with good in vitro activity and chemical stability, the high *c*Log*P* demanded by this scaffold's TpoR binding pocket interactions generated compounds with physicochemical properties (e.g., extremely low aqueous solubility) which precluded this series of analogs from further pharmaceutical development.



**Scheme 3.** Reagents and conditions: (a) i—RMgCl (2 equiv), THF, −78 °C, 1 h, 25 °C, 1 h; ii—$CH_2Cl_2$, PDC (1.2 equiv).



**Scheme 4.** Reagents and conditions: (a) i—4-butylphenylboronic acid (2 equiv), CsF (3 equiv), $((t\text{-Bu})_3P)_2Pd$ (5%), dioxane, 120 °C, 15 min; ii—$H_2$, 10% Pd/C, 2:1 MeOH/EtOAc; (b) i—aromatic aldehyde (1 equiv), $NaHSO_3$ (1.5 equiv), DMA, 140 °C, 1 h; ii—LiOH (5 equiv), EtOH, THF, 165 °C, 5 min.



**Scheme 5.** Reagents and conditions: (a) i—dibutylvinylboronic ester (1.5 equiv), $Pd(PPh_3)_2Cl_2$ (4%), $Na_2CO_3$ (7 equiv), 4:1 THF/$H_2O$, 80 °C, overnight; (b) $RuCl_3.H_2O$ (5%), $NaIO_4$ (4 equiv), $CCl_4$, 3:2 $H_2O$/MeCN, 50 °C, 2 h.

## References and notes


1. Alper, P. B.; Marsilje, T. H.; Mutnick, D.; Lu, W.; Chatterjee, A.; Roberts, M. J.; He, Y.; Karanewsky, D. S.; Chow, D.; Lao, J.; Gerken, A.; Tuntland, T.; Liu, B.; Chang, J.; Gordon, P.; Seidel, H. M.; Tian, S. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5255.
2. Revill, P.; Serradell, N.; Bolos, J. *Drugs Future* **2006**, *31*, 767.
3. Bussel, J. B.; Cheng, G.; Saleh, M. N.; Psaila, B.; Kovaleva, L.; Meddeb, B.; Kloczko, J.; Hassani, H.; Mayer, B.; Stone, N. L.; Arning, M.; Provan, D.; Jenkins, J. M. *N. Engl. J. Med.* **2007**, *357*, 2237.
4. Jenkins, J. M.; Williams, D.; Deng, Y.; Uhl, J.; Kitchen, V.; Collins, D.; Erickson-Miller, C. L. *Blood* **2007**, *109*, 4739.
5. McHutchison, J. G.; Dusheiko, G.; Shiffman, M. L.; Rodriguez-Torres, M.; Sigal, S.; Bourliere, M.; Berg, T.; Gordon, S. C.; Campbell, F. M.; Theodore, D.; Blackman, N.; Jenkins, J.; Afdhal, N. H.; Bronowicki, J. P.; DeLedinghen, V.; Dumortier, J.; Encke, J.; Germanidis, G.; Lawitz, E.; Marcellin, P.; Mills, P.; Poupon, R.; Rustgi, V.; Teuber, G.; Tran, A.; Zarski, J. P. *N. Engl. J. Med.* **2007**, *357*, 2227.
6. Erickson-Miller, C. L.; DeLorme, E.; Tian, S.-S.; Hopson, C. B.; Stark, K.; Giampa, L.; Valoret, E. I.; Duffy, K. J.; Luengo, J. L.; Rosen, J.; Miller, S. G.; Dillon, S. B.; Lamb, P. *Exp. Hematol. (New York)* **2005**, *33*, 85.
7. Duffy, K. J.; Darcy, M. G.; Delorme, E.; Dillon, S. B.; Eppley, D. F.; Erickson-Miller, C.; Giampa, L.; Hopson, C. B.; Huang, Y.; Keenan, R. M.; Lamb, P.; Leong, L.; Liu, N.; Miller, S. G.; Price, A. T.; Rosen, J.; Shah, R.; Shaw, T. N.; Smith, H.; Stark, K. C.; Tian, S. S.; Tyree, C.; Wiggall, K. J.; Zhang, L.; Luengo, J. I. *J. Med. Chem.* **2001**, *44*, 3730.
8. Compounds **9**, **22**–**24**, and **26** were assayed in the presence of 1 mM Zn rather than the 25 mM Zn levels present for the other compounds discussed in this communication. We have noted that there is usually no more than a two-fold difference between data collected under the two different conditions (data not shown).
9. Reiter, L. A.; Jones, C. S.; Brissette, W. H.; McCurdy, S. P.; Abramov, Y. A.; Bordner, J.; DiCapua, F. M.; Munchhof, M. J.; Rescek, D. M.; Samardjiev, I. J.; Withka, J. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3000.
10. Alper, P.; Marsilje, T.; Chatterjee, A.; Lu, W.; Mutnick, D.; Roberts, M. J.; He, Y. WO2007009120, 2007.
11. Marsilje, T.; Lu, W.; Alper, P.; Mutnick, D.; He, Y. WO2007022269, 2007.
12. Dyke, S. F.; White, A. W. C.; Hartley, D. *Tetrahedron* **1973**, *29*, 857.
13. Fouad, F. S.; Crasto, C. F.; Lin, Y.; Jones, G. B. *Tetrahedron Lett.* **2004**, *45*, 7753.