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Synthesis and evaluation of the anti-proliferative activity of diaryl-3-pyrrolin-2-ones and fused analogs

Patricia Mowery [a,*], Fernando Banales Mejia [b], Courtney L. Franceschi [b], Maeve H. Kean [b], Deborah O. Kwansare [b], Megan M. Lafferty [b], Namita D. Neerukonda [a], Carly E. Rolph [a,b], Nathanyal J. Truax [b], Erin T. Pelkey [b,*]

[a] Department of Biology, Hobart and William Smith Colleges, Geneva, NY 14456, USA
[b] Department of Chemistry, Hobart and William Smith Colleges, Geneva, NY 14456, USA

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ABSTRACT

Analogs containing a central 3-pyrrolin-2-one core with different methoxyphenyl and/or indole substituents were prepared and tested for anti-proliferative activity in U-937 cells. The most efficacious analogs were non-rigid, (non-fused) contained methoxyaryl groups located at the 4-position, and contained either methoxyaryl or indole groups located at the 3-position. Both the number of methoxy groups contained in the substituents and the particular location of the indole rings with respect to the lactam carbonyl had significant affects on anti-proliferative activity. This work provides a framework to better understand structure-activity relationships for inducing anti-proliferative activity in diaryl heterocyclic scaffolds.

Certain structural motifs are repeatedly found in biologically active small molecules. These reoccurring substructures[1] or scaffolds[2] were first coined as "privileged structures"[3–6] by Evans. Privileged structures provide a backbone upon which chemical motifs can be added to alter ligand specificity and activity. The presence of two proximal aryl rings is part of three common privileged structural motifs (Fig. 1): biphenyl, diarylmethane, and vicinal diaryl (two aryl groups located vicinal on a central ring). Diaryl-containing privileged structures have proven their importance in a number of drug discovery programs.[6]

Numerous biologically active molecules contain a privileged structure of a central nitrogen heterocycle substituted with two adjacent aryl groups (vicinal diaryl substructure) (Fig. 2).[7] Two such nitrogen heterocyclic ring systems, maleimides and 3-pyrrolin-2-ones, have been studied in some detail. Polymethoxylated maleimides (*e.g.*, **2**),[8] 3-pyrrolin-2-ones (*e.g.*, **3**),[9] and pyrroles (not shown)[10,11] have been investigated as *cis*-constrained analogs of the promising anti-cancer agent, combretastatin A-4.[12] SB-216763 (**4**) is an ATP-competitive inhibitor of glycogen synthase kinase.[13] Bisindolemaleimide (**5**)[14] is a potent inhibitor of protein kinase C, which has inspired a large number of follow-up studies on bisindolemaleimide analogs.[15–17] Indole-substituted arylmaleimides (*e.g.*, **6**)[18] and aryl-3-pyrrolin-2-ones (*e.g.*, **7**)[19] have shown anti-angiogenic activity, while fused bisindolemaleimide **8** (arcyriaflavin A) and 3-pyrrolin-2-one **9** (K-252c) are natural products with demonstrated antiviral[20] and protein kinase inhibitory activity,[21] respectively. Common aryl substituents found across this sample of biologically active nitrogen maleimides and 3-pyrrolin-2-ones include polymethoxyaryl groups and indole rings.

Building on our expertise in preparing aryl-substituted 3-pyrrolin-2-ones,[22–25] we systematically studied the effects of changing the aryl groups around the central 3-pyrrolin-2-one ring on cancer cell viability. In our study (Fig. 3), we prepared a small library of analogs that differed in the following ways: (i) analogs with different numbers (and locations) of aryl groups and methoxy substituents around the aryl periphery; (ii) analogs with indole groups located at different positions; and (iii) cyclized analogs (central ring fusion).

We started by preparing 4-aryl-substituted 3-pyrrolin-2-ones from known tetramic acid tosylate **10** (Scheme 1).[23] This starting material has previously been proven to be viable in Suzuki-Miyaura cross-coupling reactions. Indeed, treatment of **10** with arylboronic and Pd(dppf)Cl_2 in the presence of Cs_2CO_3 gave **11c** and **11d** in modest yields.

The preparation of 3,4-diaryl-3-pyrrolin-2-ones started with the synthesis of 3-aryl- and 3-indolyltetramic acids **15** adapting our recently published method (Scheme 2).[25] The three-step procedure included DCC-mediated amide coupling of arylacetic acids **12**

* Corresponding authors.
E-mail addresses: mowery@hws.edu (P. Mowery), pelkey@hws.edu (E.T. Pelkey).

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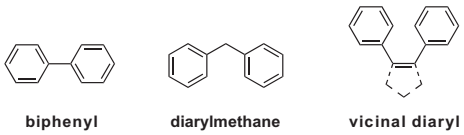
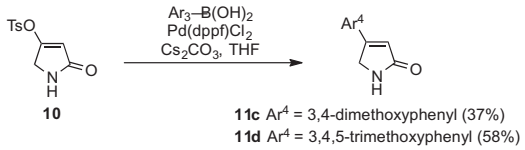


Fig. 1. "Privileged" diaryl-containing structural motifs.

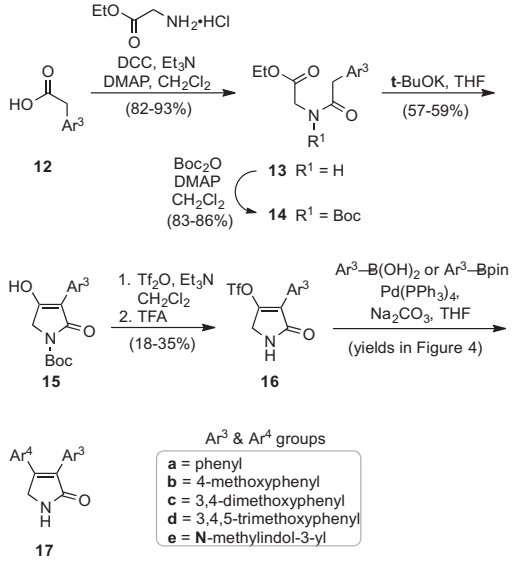


Scheme 1. Synthesis of 4-aryl-3-pyrrolin-2-ones.

with ethyl glycinate giving amidoesters **13**, Boc-protection to **14** with Boc_2O promoted by DMAP, and a Dieckmann cyclization to tetramic acids **15** promoted by *t*-BuOK. The tetramic acids **15** were then converted into the corresponding tetramic acid triflates **16** by treatment with Tf_2O followed by removal of the Boc-protecting group with TFA. Suzuki-Miyaura cross-coupling of **16** with arylboronic acids or arylboronic acid pinacol esters gave the desired 3,4-diaryl-3-pyrrolin-2-ones **17** (Fig. 4). Given that there are two different aryl/heteroaryl rings present in most of the analogs, the compound numbers assigned to each analog include two letters with each letter denoting one of the aryl rings. For example, **17ea** is an analog with a "*N*-methylindol-3-yl" substituent at the 3-position and a "phenyl" substituent at the 4-position.

We have previously found that electron-rich diaryl-substituted 3-pyrrolin-2-ones can be transformed into their corresponding ring fused analogs using the oxidant, phenyliodine(III)bis(trifluoroacetate) (PIFA).[25] Using this strategy, benzo[*a*]carbazole **18ec** was prepared using an oxidative cyclization of **17ec** (Scheme 3). Treatment of **17ec** with PIFA and $BF_3{\cdot}Et_2O$ at −40 °C gave **18ec** in 70% yield. An additional ring fused analog, **18cc**, was available from a prior study.[25]

To determine the potency of the various analogs, compounds were tested on the human promonocytic cell line, U-937,[26] via MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay over 48 h.[27] IC_{50} values were defined as the analog concentration at which cell viability reduced to 50% compared to mock-treated cells. The biological data for the compounds are presented in a graphical format in two figures: (i) indole-containing analogs (Fig. 5) and (ii) polymethoxyaryl-containing analogs (Fig. 6). The analogs with the most potent IC_{50} values within each figure included one indole-containing analog, **17ec** (10 μM ± 2), and two polymethoxyaryl-containing analogs, **17bb** (13 μM ± 2)



Scheme 2. Synthesis of 3,4-diaryl-3-pyrrolin-2-ones.

and **17dd** (11 μM ± 3). The IC_{50} values for these three compounds were statistically equivalent ($p > 0.35$).

In examining the results with the indole-containing analogs (Fig. 5), it is clear that the location of the indole substituent on the 3-pyrrolin-2-one central core ring impacts cell viability. Analogs with indole substitution at C4, **11e**[28] and **17ce**, were inactive, as defined as an $IC_{50} > 100$ μM. Two of the analogs with indole substitution at C3, **17ec** (10 μM ± 2) and **17ed** (38 μM ± 9), showed

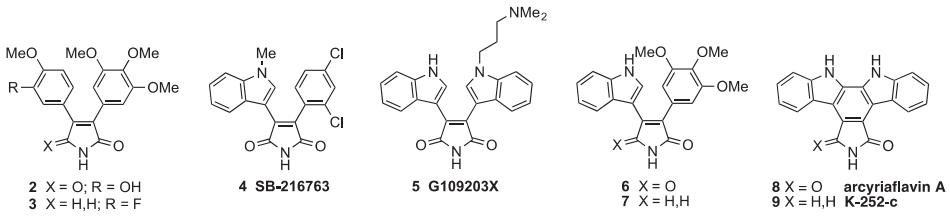


Fig. 2. Biologically active diaryl-substituted maleimides and 3-pyrrolin-2-ones.

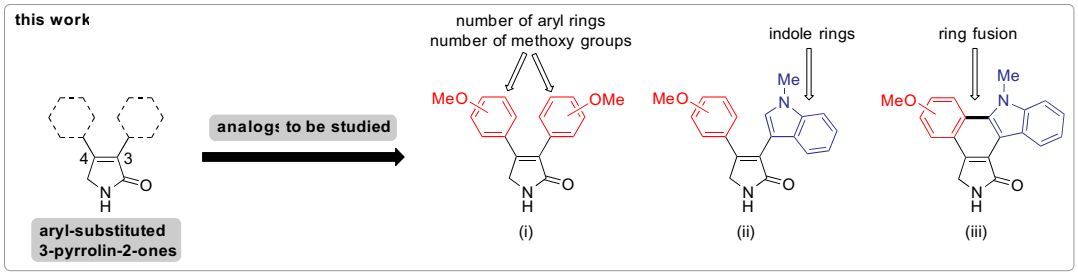


Fig. 3. Proposed aryl-substituted 3-pyrrolin-2-one targets for anti-proliferative studies.