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Discovery of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. Part 1: Structure–activity relationships of the 1- and 3-positions

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ABSTRACT

1-Benzoyl-3-cyanopyrrolo[1,2-*a*]quinoline (**2a**) was identified as a novel apoptosis inducer through our caspase- and cell-based high-throughput screening assay. Compound **2a** had good activity against several breast cancer cell lines but was much less active against several other cancer cell lines. SAR studies of **2a** found that substitution at the 4-position of the 1-benzoyl group was important for activity. Replacing the 3-cyano group by an ester or ketone group led to inactive compounds. Interestingly, 4-substituted analogs such as 1-(4-(1*H*-imidazol-1-yl)benzoyl)-3-cyanopyrrolo[1,2-*a*]quinoline (**2k**) were found to be broadly and highly active in the caspase activation assay as well as in the cell growth inhibition assay with low nM EC_{50} and GI_{50} values in human breast cancer cells T47D, human colon cancer cells HCT116, and hepatocellular carcinoma cancer cells SNU398. Compound **2a** was found not to inhibit tubulin polymerization up to 50 μM, while **2k** was found to inhibit tubulin polymerization with an IC_{50} value of 5 μM, indicating that certain substituents at the 4-position of the 1-benzoyl group can change the mechanism of action.

Cancer is a major worldwide problem and is the second leading cause of mortality in developed countries.[1] Since many of the current treatments have problems with toxicity and drug-resistance, there is a strong demand for the discovery and development of effective new cancer therapies.[2] The traditionally prescribed chemotherapeutic agents that bind tubulin, including paclitaxel and vinblastine,[3–5] and new compounds such as epothilone,[6] have suffered from dose-limiting neurological and bone marrow toxicity. More recently, numerous kinase inhibitors have been discovered and several have been successfully developed, including Gleevec,[7] Iressa,[8] Tarceva,[9] Tykerb,[10] and Sutent,[11] with improved efficacy and less toxicity.

Identification of compounds that activate and promote apoptosis is another attractive approach for the discovery and development of potential anticancer agents. The acquisition of resistance to apoptosis is one of the hallmarks in the transformation of normal cells to cancerous[12] and apoptosis may also be involved in the regulation of metastasis.[13] Further, it has been reported that the antitumor efficacy of several chemotherapeutic agents correlated to their apoptosis-inducing ability.[14] It is known that apoptosis proceeds through a family of cysteine proteolytic enzymes known as caspases.[15] Activation of these proteases, which are normally present within cells as inactive zymogens, results in the cleavage of multiple protein substrates inside cells and leads to irreversible apoptotic cell death.[16] Among the caspases, caspase-3, -6, and -7 have been identified as important downstream effector caspases that lead to apoptotic cell death.[17]

We have reported the development of a cell-based Anti-cancer Screening Apoptosis Program (ASAP) HTS technology to identify apoptosis inducers using our novel fluorogenic caspase-3 substrates.[18,19] Applying this HTS assay, we have identified several series of novel apoptosis inducers. 4-Aryl-4*H*-chromenes, such as 2-amino-3-cyano-7-dimethylamino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-chromene (**1a**), have been identified as a class of potent apoptosis inducers (Chart 1) binding to tubulin,[20] and several of them have demonstrated vascular disrupting activity (VDA) with good efficacy in several anticancer animal models.[21,22] Gambogic acid (**1b**) was discovered as a fast and potent apoptosis inducer,[23] and the transferrin receptor has been identified as the molecular target.[24] 3-Aryl-5-aryl-1,2,4-oxadiazoles, exemplified by 5-(3-chlorothiophen-2-yl)-3-(4-trifluoromethylphenyl)-1,2,4-oxadiazole (**1c**) were found to induce apoptosis selectively in certain tumor types,[25] and TIP47, an insulin-like growth factor II (IGF II) receptor binding protein, has been identified as the molecular target.[26] More recently, we have reported the discovery of 4-anilino-2-(2-pyridyl)pyrimidines, exemplified by 4-(2,5-dimethoxyanilino)-2-(2-pyridyl)-6-(trifluoromethyl)pyrimidine (**1d**) as

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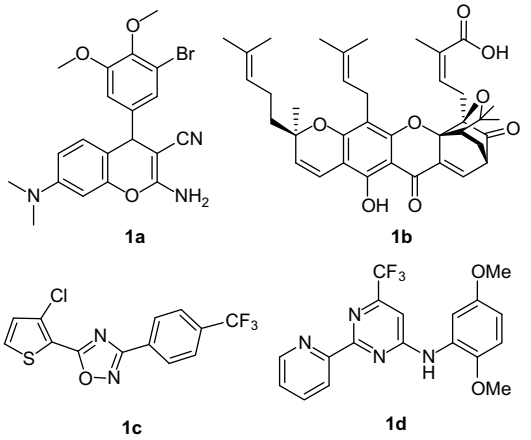
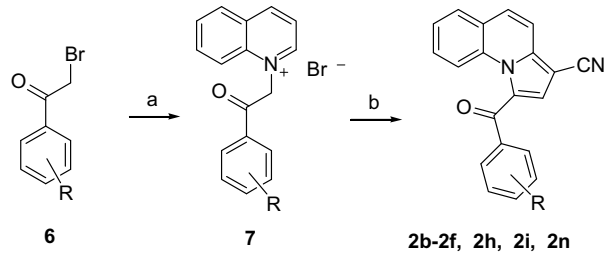


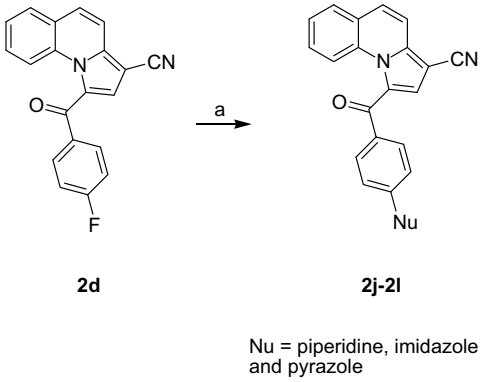
Chart 1.

potent apoptosis inducers.[27] Herein, we report the discovery of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinoline (**2a**) as a potent apoptosis inducer and structure–activity relationship (SAR) study of the 1 and 3-positions of **2a**.

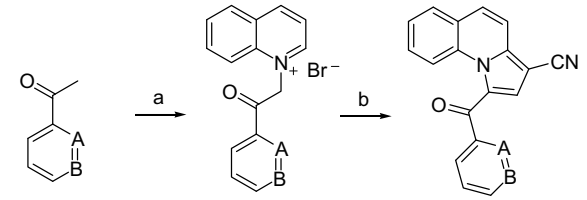
The original hit, 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinoline (**2a**), as well as 3-acetyl-1-(4-methylbenzoyl)-pyrrolo[1,2-*a*]quinoline (**4**) and 3-ethyl carboxylate-1-(3-methoxybenzoyl)-pyrrolo[1,2-*a*]quinoline (**5**) were obtained from a commercial compound library, structure verified by ^{1}H NMR. 1-Benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines were generally prepared in two steps in good yield, starting from the appropriate substituted 2-bromoacetylphenone, quinoline and acrylonitrile according to literature procedure (Scheme 1).[28] Compounds **2b–2f, 2h, 2i**, and **2n** were all prepared in this manner starting from the corresponding commercially available 2-bromoacetylphenones (**6**) by reaction with quinolines to give the quinolinium salts (**7**). This was followed by cyclization with acrylonitrile in the presence of an oxidant, such as tetrapyridinecobalt (II) dichromate (TPCD, $Co(II)Py_4(HcrO_4)_2$) or manganese(IV) oxide (MnO_2) and a base.[29] Compounds **2j–2l** were prepared from 3-cyano-1-(4-fluorobenzoyl)-pyrrolo[1,2-*a*]-quinoline (**2d**) by nucleophilic substitution with the appropriate nucleophile (Scheme 2).[30] The pyridyl analogs **2o–2p** were prepared in a two step process involving reaction of the appropriate acetylpyridine (**8o–8p**) with iodine and quinoline to form the quinolinium salts (**9o–9p**), which are then rapidly cyclized with TPCD (Scheme 3). Compound **2g** was made from 3-cyano-1-(4-nitrobenzoyl)-pyrrolo[1,2-*a*]quinoline (**2f**) by hydrogenation with palladium on carbon under standard conditions. The hydroxyl compounds **3a–3c** were prepared in high yield by the reaction of the corresponding benzoyl compounds **2b, 2i**, and **2l** with sodium borohydride in methanol (Scheme 4).



Scheme 1. Reagents and conditions: (a) quinoline, CH_3CN, 85 °C, 4–6 h; (b) acrylonitrile, TPCD, DMF, Na_2CO_3, 95 °C, 5 h or acrylonitrile, MnO_2, DMF, Et_3N, 95 °C, 5 h.



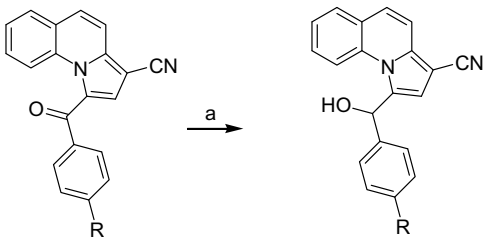
Scheme 2. Reagents and conditions: (a) nucleophile , DMF, K_2CO_3, 160 °C, 20 h.



Scheme 3. Reagents and conditions: (a) quinoline, iodine, 105 °C, 2 h; (b) acrylonitrile, TPCD, DMF, Na_2CO_3, 95 °C, 2.5 h.

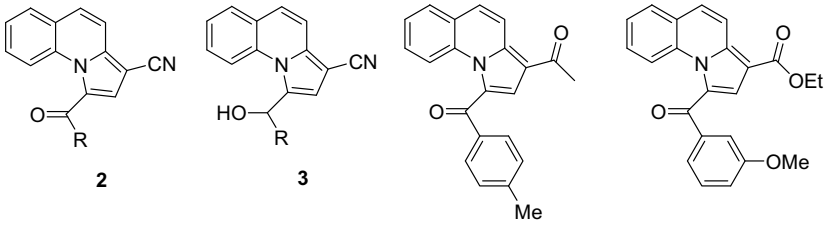
The apoptosis inducing activity of these 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines was measured by our proprietary cell- and caspase-based HTS assay as described previoiusly[20] in human breast cancer cells T47D, human colon cancer cells HCT116 and hepatocellular carcinoma cancer cells SNU398, and the results are summarized in Table 1. The original hit, 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinoline (**2a**), has an EC_{50} for caspase activation of 0.078, 5.5, and 5.2 μM in T47D, HCT116, and SNU398 cells, respectively. Compound **2a** was then further tested for growth inhibition in a panel of human cancer cells to confirm the selectivity. It was found that **2a** is active in several human breast cancer cell lines, including SKBr3, ZR75-1, and Bt474, with GI_{50} values ranging from 70 to 240 nM. In addition, **2a** was tested in colon (DLD-1, HT29), lung (H1299), leukemia (K562), and lymphoma (Namalwa and Raji) cancer lines and found to have GI_{50} values ranging from 1.2 to 6.0 μM, indicating that **2a** is selective towards breast cancer cells.

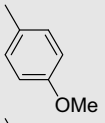
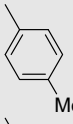
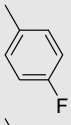
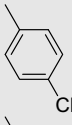
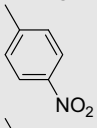
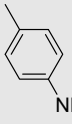
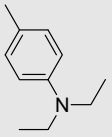
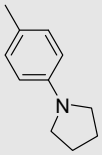
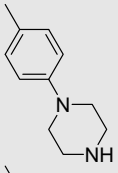
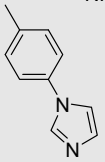
By maintaining the pyrrolo[1,2-*a*]quinoline group of **2a**, the SAR of the benzoyl group was explored, beginning with mono-substitu-



Scheme 4. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 20 h.

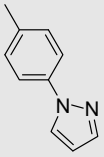
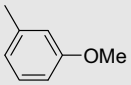
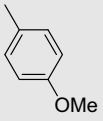
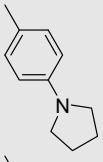
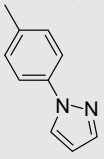
Table 1
SAR of the 1- and 3-positions of pyrrolo[1,2-*a*]quinolines in the caspase activation assay.



Compound	R	EC_{50} (μM)[a]		
		T47D	HCT116	SNU398
2a		0.078 ± 0.002	5.5 ± 0.069	5.2 ± 0.13
2b		0.28 ± 0.017	0.28 ± 0.024	0.18 ± 0.027
2c		0.93 ± 0.17	4.2 ± 0.7	2.7 ± 0.034
2d		0.036 ± 0.011	1.2 ± 0.059	0.88 ± 0.21
2e		0.049 ± 0.011	>10	>10
2f		2.8 ± 0.17	>10	>10
2g		0.17 ± 0.022	0.24 ± 0.044	0.20 ± 0.036
2h		0.10 ± 0.019	0.37 ± 0.005	0.26 ± 0.004
2i		0.30 ± 0.031	0.58 ± 0.019	0.51 ± 0.053
2j		>10	>10	>10
2k		0.034 ± 0.001	0.074 ± 0.011	0.039 ± 0.001

(*continued on next page*)

Table 1 (*continued*)

Compound	R	EC_{50} (μM)[a]		
		T47D	HCT116	SNU398
2l		0.041 ± 0.003	0.096 ± 0.018	0.057 ± 0.004
2m		0.14 ± 0.014	2.5 ± 0.046	2.7 ± 0.064
2n		0.17 ± 0.014	1.7 ± 0.42	1.6 ± 0.51
2o		0.040 ± 0.055	1.9 ± 0.27	1.6 ± 0.24
2p		0.69 ± 0.008	3.7 ± 0.52	2.6 ± 0.097
3a		0.22 ± 0.017	0.24 ± 0.007	0.14 ± 0.012
3b		0.21 ± 0.044	0.32 ± 0.011	0.30 ± 0.028
3c		0.16 ± 0.005	0.55 ± 0.054	0.35 ± 0.062
4	NA	>10	>10	>10
5	NA	>10	>10	>10

[a] Data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).

tions at the 4-position. Introduction of a 4-fluoro substituent gave the analog **2d**, which maintained selectivity across the cancer cell lines and was 2-fold more potent than **2a** in T47D cells. The 4-chloro analog **2e** is similar in potency to **2d** in T47D cells, suggesting that a small electron withdrawing substituent at the 4-position maintains potency and selectivity. Interestingly, the methyl analog **2c** was >11-fold less active than **2a** in T47D cells and the nitro analog **2f** was >35-fold less active than that of **2a**.

The SAR was further explored by introducing substituents in the 2- or 3-positions of the benzoyl group. The 2-methyl analog **2m** was found to be a potent and selective compound that is <2-fold less active than **2a** and >6-fold more active than **2c**, indicating that substitution at the 2-position is well tolerated. The 2-pyridyl analog **2o** was almost 2-fold more potent than **2a**. In addition, **2o** maintained good selectivity with EC_{50} values of 1.9 and 1.6 μM for HCT116 and SNU398, respectively. The 3-methoxy analog **2n** was >2-fold less active than **2a**. Replacing the phenyl ring with a 3-pyridyl group resulted in **2p**, which was >8-fold less active than that of **2a**.

Interestingly, the 4-methoxy analog **2b** had EC_{50} values of 0.28, 0.28, and 0.18 μM in T47D, HCT116, and SNU398 cells, respectively. The caspase activation data for **2b** indicates that this compound is broadly active and suggests a potential change of mechanism of action. The amino analog **2g** was also active in all three-cell lines and was about as active as **2b** in T47D cells. The diethylamino analog **2h** was found to be >2-fold more potent than **2b** in T47D cells and suggested that a large group at the 4-position might increase activity. The pyrrolidine analog **2i** was similar in potency to **2b**. The heterocyclic imidazole analog **2k** was >7-fold more active than **2b** with an EC_{50} value of 0.034 μM for T47D cells. The pyrazole analog **2l** was also highly potent with an EC_{50} value of 0.041 μM, indicating that an aromatic, five-member nitrogen het-

erocycle is preferred in the 4-position. In comparison, the piperidine analog **2j** was found to be inactive up to 10 μM for the three cell lines tested.

In an effort to improve the solubility profile, the more rigid carbonyl linker of the benzoyl group was reduced to a more flexible hydroxyl group. Analog **3a** was similar in potency to **2b**, indicating that changing the carbonyl to a hydroxyl group is tolerated. Similarly, the hydroxyl analog **3b** was about as active as the carbonyl analog **2i**, while analog **3c** was 4-fold less active than **2l**.

The SAR at the 3-position of the pyrrolo[1,2-*a*]quinoline structure was also investigated. Replacing the 3-cyano group of **2c** with an acetyl group gave the analog **4**, which was found to be inactive in the caspase activation assay up to 10 μM. Additionally, analog **5**, with the 3-cyano group of **2n** replaced with an ethyl ester group, was found to be inactive, indicating that the cyano group at the 3-position might be essential for activity.

Selected compounds were also tested by the traditional cell growth inhibition assay (GI_{50}) to confirm that the active compounds can inhibit tumor cell growth. The growth inhibition assays in T47D, HCT116, and SNU398 cells were run in a 96-well microtiter plate as described previously.[27] The GI_{50} values are summarized in Table 2. Compound **2a** was found to have selectivity similar to the EC_{50} caspase assay with GI_{50} values of 0.070, 5.8, and 2.0 μM in T47D, HCT116, and SNU398 cells, respectively. In general, compounds **2b, 2g, 2i, 2l**, and **2m** were more sensitive to T47D and SNU398 cells, than to HCT116 cells. Compounds **2b** and **2i** both had GI_{50} values <100 nM in the T47D cells. Compound **2k**, which was the most active compound in the caspase assay, was also the most active in the GI_{50} assay with values of 0.041, 0.065, and 0.059 μM for T47D, HCT116, and SNU398 cells, respectively.

Compounds **2a** and **2k** were characterized by cell cycle analysis[20] in HCT116 cells and found to arrest cell in G_2/M and induce apoptosis. Since tubulin inhibitors are known to arrest cells in G_2/M, we tested several compounds in a tubulin polymerization assay[31] in an attempt to differentiate the mechanism of action of the broad active vs. the selective compounds. Compound **2a**, which was active against breast cancer cells but much less active against several other cancer cell lines, was found to be inactive in the tubulin polymerization assay at up to 50 μM. Compounds **2l** and **2k**, both of which were broadly active against the three cancer cell lines tested, were found to be active in the tubulin polymerization assay, with IC_{50} values of 1 and 5 μM, respectively, indicating that compounds **2l** and **2k** and other broadly active compounds in this series most probably induce apoptosis through inhibition of tubulin polymerization. These data confirmed that with different substituents in the 4-position of the 1-benzoyl group, the selective compounds and non-selective compounds have different mechanism of actions. We have observed previously a similar change from selective compounds to non-selective compounds and change of mechanism of action for a series of apoptosis inducing 4-anilino-2-(2-pyridyl)pyrimidines with different substituents in the 4-anilino group.[27]

Table 2
Inhibition of cell growth of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines.

Compound	GI_{50} (μM)[a]		
	T47D	HCT116	SNU398
2a	0.070 ± 0.015	5.8 ± 0.13	2.0 ± 0.50
2b	0.071 ± 0.008	0.49 ± 0.008	0.12 ± 0.004
2g	0.47 ± 0.056	1.2 ± 0.11	0.42 ± 0.086
2i	0.075 ± 0.014	0.25 ± 0.038	0.14 ± 0.013
2k	0.041 ± 0.008	0.065 ± 0.015	0.059 ± 0.009
2l	0.072 ± 0.026	0.24 ± 0.10	0.036 ± 0.007
2m	0.087 ± 0.013	1.6 ± 0.18	0.73 ± 0.13

[a] Data are the mean of three or more experiments and are reported as mean ± standard error of the mean (SEM).

In conclusion, we have discovered and explored the SAR of the apoptosis inducing 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines by modifying the 1 and 3-positions. It was found that small electron withdrawing groups at the 4-position of the 1-benzoyl group like F and Cl are preferred to maintain potency and selectivity in the caspase activation assay. Substitution at the 2- or 3-positions of the benzoyl group also resulted in active compounds. In addition, the phenyl ring could be replaced by a 2-pyridyl group. The 3-cyano group was found to be important for activity. Interestingly, substitution at the 4-position of the 1-benzoyl group with an imidazole (**2k**) or pyrazole (**2l**) group resulted in highly active compounds with a different caspase activation profile. These compounds were broadly active and induced apoptosis by inhibiting tubulin polymerization. In addition, hydroxyl analogs were also active offering the potential for improving aqueous solubility. Through SAR studies of the 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines, compound **2k** was identified, which has low nanomolar potency in both the caspase activation assay and growth inhibition assay and is significantly more potent than the initial hit **2a**. Additional SAR studies of the 4-, 5-, 6-, 7-, and 8-positions of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines will be reported in future publications.

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