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Design, synthesis, and in vitro antitumor activity of new 1,4-diarylimidazole-2-ones and their 2-thione analogues

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Abstract—A series of new 1,4-diarylimidazol-2(*3H*)-one derivatives and their 2-thione analogues has been prepared and evaluated in vitro for antitumor activity against the NCI human cancer cell panel. Compounds bearing a 3,4,5-trimethoxyphenyl ring linked to either N-1 or C-4 position of the imidazole core demonstrated an interesting profile of cytotoxicity with preferential activity against leukemic cell lines. Compound **13** exhibited a potent antitumor activity against MOLT-4 (GI_{50} = 20 nM) and SR (GI_{50} = 32 nM) cell lines.

The discovery of anticancer properties of the combretastatins, a group of antimitotic agents isolated from the bark of the South African willow tree *Combretum caffrum* Kuntz,[1] has attracted considerable interest of medicinal chemists in the design of analogues as novel antitumor agents. Combretastatin A-4 (CA-4, Fig. 1) appears to be the most active compound in the group, showing potent inhibitory activity against a variety of human cancer cells, including multi-drug resistant cell lines.[2] CA-4 is one of the most potent antimitotic agents and binds to tubulin on the colchicine binding site.[3] The low water solubility of CA-4 limits its efficacy in vivo, and several attempts have been made to produce an active water-soluble derivative.[4] The most effective is the disodium phosphate salt and is the form of CA-4 currently in Phase II clinical trials.[5] Moreover, the *Z*-configured ethenyl bridge of CA-4 is prone to isomerize to the *E*-form during storage and administration leading to dramatic reduction in both antitubulin activity and cytotoxicity.[5a,6] Therefore, considerable efforts have gone into modifying CA-4 and discovering its new possible bioisosteres, based on replacement of the *Z*-restricted double bond.[7] Many synthetic analogues have been developed following the strategy of design of two-atom bridgehead analogues utilizing 1,2-oriented heterocycles.[8] In contrast, a limited number of analogues have been successfully designed following the strategy of three-atom bridgeheads 1,3-oriented with a linear- or heterocycle-linker inserted between the two aryl rings of combretastatins. A series of chalcones, developed by Edwards et al.,[9] and a large collection of oxazoline and oxadiazoline derivatives, analogues of A-105972 obtained in the Abbott Laboratories,[10] constituted some examples of compound designed following this strategic approach (Fig. 1).

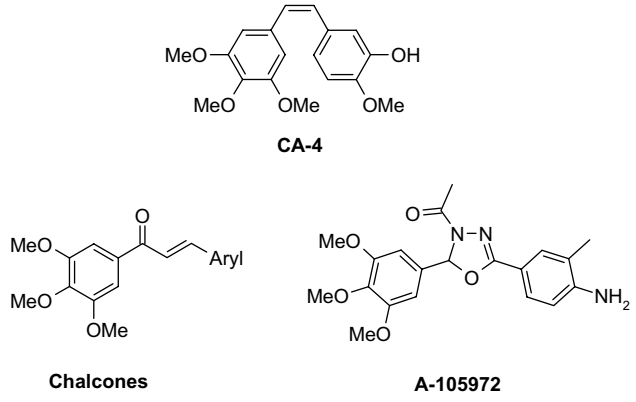

Figure 1. CA-4 and three-atom bridgehead 1,3-oriented analogues.

In our efforts to discover new active antitumor agents, we were particularly interested in the imidazole ring. Basic nitrogen atoms of the imidazole ring may lead to compounds with decreased lipophilicity that can be formulated into water-soluble salts to give improved pharmacokinetic properties. As far as the imidazole derivatives are concerned, a literature survey in the field

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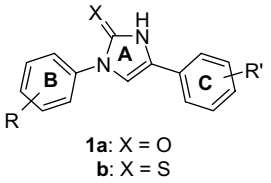


Figure 2.

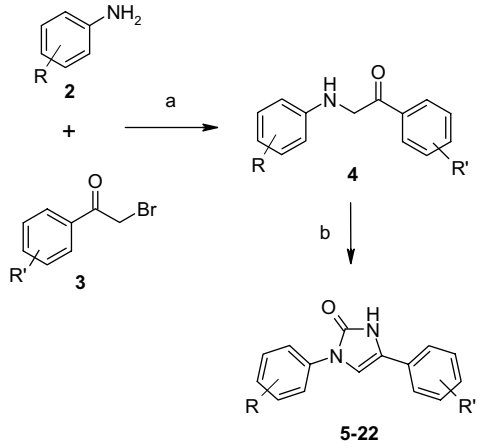
of synthetic antitumor agents revealed that there was an apparent lack of imidazolone-type compounds. Recently a trisubstituted imidazolone derivative has been reported to induce apoptosis in human leukemia cells.[11]

Based on these considerations, we designed an easy synthetic approach for preparing of 1,4-diaryl-1*H*-imidazol-2(3*H*)-ones **1a** in order to study their antitumor activity (Fig. 2).

In this communication, we wish to report the synthesis and preliminary anticancer activity of a series of new imidazolone derivatives, and their 2-thione analogues **1b** (Fig. 2). These compounds have been designed following the strategy of three-atom bridgehead 1,3-oriented CA-4 analogues, where the imidazole core (ring A) serves as a linker between functionalized B- and C-rings. Some recent reviews have meticulously summarized structure activity relationships of CA-4 and its synthetic analogues,[12] and outlined that a 3,4,5-trimethoxyphenyl ring was essential for potent antitumor activity. Therefore, we started our study from 4-phenyl-1-(3,4,5-trimethoxyphenyl)-1*H*-imidazol-2(3*H*)-one **5** and designed systematic structural variations on 1,3-oriented phenyl rings. The antiproliferative properties of these compounds against the NCI human cancer cell line panel were evaluated.

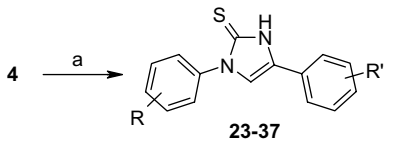
The synthesis of some 1- or 4-arylimidazol-2(3*H*)-ones has been described.[13] The only reported 1,4-diaryl derivative, namely the 1,4-diphenyl-1*H*-imidazol-2(3*H*)-one, has been synthesized by the acid promoted dehydration of the corresponding 4-hydroxy-2-imidazolidinone.[14] In our approach, 1,4-diaryl-1*H*-imidazol-2(3*H*)-one system was conveniently assembled by first setting a functionalized intermediate, bearing substitution patterns on pendant B- and C-rings, and then closing the central A-ring. Compounds **5**–**22** were prepared as shown in Scheme 1. Coupling of an aniline **2**, from which the B-ring was derived, with a phenacyl bromide **3**, bearing a substitution pattern desired for the C-ring, afforded a wide array of *N*-arylphenacylamines **4**. Compounds **4** represent an easily available key intermediate for introduction of opportunely substituted B- and C-rings. The reaction was performed at room temperature, in anhydrous methanol and in the presence of two equivalents of sodium bicarbonate. *N*-Arylphenacylamines **4** were then reacted with a large excess of potassium cyanate in acetic acid at 60–65 °C to effect closure of the imidazolone ring affording compounds **5**–**22** in 56–92% yields.[15]

The imidazole-2-thione analogues were prepared by some modification of established procedures[16] (Scheme 2).



5: R = 3,4,5-$(MeO)_3$; R' = H
6: R = 3,4,5-$(MeO)_3$; R' = 4-F
7: R = 3,4,5-$(MeO)_3$; R' = 4-Cl
8: R = 3,4,5-$(MeO)_3$; R' = 4-MeO
9: R = 3,4,5-$(MeO)_3$; R' = 3,4-$(MeO)_2$
10: R = 3,4-$(MeO)_2$; R' = 4-Cl
11: R = 3,4-$(MeO)_2$; R' = 4-MeO
12: R = 4-F; R' = 3,4,5-$(MeO)_3$
13: R = 4-Cl; R' = 3,4,5-$(MeO)_3$
14: R = 4-MeO; R' = 3,4,5-$(MeO)_3$
15: R = 3,4-$(MeO)_2$; R' = 3,4,5-$(MeO)_3$
16: R = 3-Cl-4-MeO; R' = 3,4,5- $(MeO)_3$
17: R = 3,4-Cl_2; R' = 3,4,5-$(MeO)_3$
18: R = 4-Cl; R' = 3,4-$(MeO)_2$
19: R = 4-MeO; R' = 3,4-$(MeO)_2$
20: R = 3-Cl-4-MeO; R' = 3,4-$(MeO)_2$
21: R = 3-Cl-4-MeO; R' = 4-Cl
22: R = 4-Cl; R' = 3,4-Cl_2

Scheme 1. Synthesis of *N*-arylphenacylamines **4** and 1,4-diarylimidazol-2-ones **5**–**22**. Reagents and conditions: (a) $NaHCO_3$, MeOH, 25 °C, 16 h; (b) KOCN, AcOH, 60–65 °C, 1 h.



23: R = 3,4,5-$(MeO)_3$; R' = H
24: R = 3,4,5-$(MeO)_3$; R' = 4-Cl
25: R = 3,4,5-$(MeO)_3$; R' = 4-MeO
26: R = 3,4,5-$(MeO)_3$; R' = 3,4-$(MeO)_2$
27: R = 3,4-$(MeO)_2$; R' = 4-Cl
28: R = 3,4-$(MeO)_2$; R' = 4-MeO
29: R = 4-Cl; R' = 3,4,5-$(MeO)_3$
30: R = 4-MeO; R' = 3,4,5-$(MeO)_3$
31: R = 3,4-$(MeO)_2$; R' = 3,4,5-$(MeO)_3$
32: R = 3-Cl-4-MeO; R' = 3,4,5-$(MeO)_3$
33: R = 4-Cl; R' = 3,4-$(MeO)_2$
34: R = 4-MeO; R' = 3,4-$(MeO)_2$
35: R = 3-Cl-4-MeO; R' = 3,4-$(MeO)_2$
36: R = 3-Cl-4-MeO; R' = 4-Cl
37: R = 4-Cl; R' = 3,4-Cl_2

Scheme 2. Synthesis of 1,4-diarylimidazole-2-thiones **23**–**37**. Reagents and conditions: (a) NH_4SCN, 10% aq HCl, reflux, 1.5 h.

Thus, upon reaction between *N*-arylphenacylamines **4** and ammonium thiocyanate in boiling 10% hydrochloric acid, compounds **23**–**37** were obtained in 64–86% yields.[17] Analytical and spectral data accounted for the assigned structures.

Synthesized compounds were submitted to the National Cancer Institute (NCI, Bethesda, MD) for the human

tumor cell screen. Selected compounds were tested initially at a single high dose (10^{-5} M) in the full NCI 60 cell panel.[18]

Only compounds which satisfy pre-determined threshold inhibition criteria will progress to evaluation in the same full panel using five concentrations at 10-fold dilutions, ranging from 10^{-4} to 10^{-8} M. For each compound in the 5-dose screen, anticancer activity was deduced from dose–response curves and expressed by three parameters (GI_{50}, TGI, LC_{50}) calculated for each cell line. The GI_{50} value indicates the concentration of the compound required to cause 50% inhibition of net cell growth. The TGI value represents the concentration of the compound resulting in total inhibition of net cell growth. The LC_{50} value refers to the concentration of the compound leading to 50% net cell death. Moreover, for each antitumor activity parameter, mean graph midpoint (MG_MID) was calculated giving an averaged activity parameter over all cell lines. For the calculation of MG_MID, insensitive cell lines were included with the highest concentration tested.

An overview of antiproliferative activities of imidazole derivatives compared to the reference compound CA-4 is reported in Table 1. Tested compounds show moderate to significant cytotoxicity, and preferential growth inhibitory activity against cell lines of the leukemia sub-panel. The mean GI_{50} values across the range of compounds are an unremarkable 10–100 μM; however, selective cytotoxic effects are elicited depending on substitution pattern of these new imidazole derivatives. The most interesting series of compounds are those bearing a 3,4,5-trimethoxyphenyl ring linked to either N-1 or C-4 position of imidazole core. Replacement of the 2-carbonyl function of imidazole ring by 2-thiocarbonyl always results in modification of cell chemosensitivity.

Table 1. Overview of antiproliferative activities of imidazole derivatives and CA-4 against the NCI human cancer cell panel[a]

Compound	5	7	11	13	16	22	31	32	33	35	36	CA-4[b]
Panel/cell line												
Leukemia												
CCRF-CEM	<4	>8.0	<4	<4	<4	4.4	<4	6.2	<4	<4	4.2	7.0
HL-60 (TB)	4.2	<4	4.4	6.4	<4	4.5	<4	<4	5.5	<4	<4	7.5
MOLT-4	<4	<4	5.8	7.7	<4	4.7	5.2	<4	<4	4.1	4.4	7.0
RPMI-8226	<4	4.9	<4	<4	<4	4.2	<4	5.3	5.4	<4	4.3	6.8
SR	<4	<4	7.0 (6.2)[c]	7.5 (4.4)[c]	4.3	5.3 (4.8)[c]	5.6 (5.1)[c]	nt[d]	5.5	<4	nt	6.9 (4.1)[c]
Non-small cell lung cancer												
EKVX	4.6	4.5	<4	<4	<4	4.5	<4	4.4	4.9	4.4	4.4	6.4
HOP-92	4.7	nt	<4	<4	4.8	4.8	<4	4.5	6.5 (5.1)[c]	4.4	4.8	6.7 (4.4)[c]
Colon cancer												
HCT-116	4.2	4.5	<4	<4	<4	4.8	<4	4.6	5.4	<4	4.3	7.5
HCT-15	4.1	<4	<4	<4	<4	<4	<4	<4	5.3	<4	<4	7.5
CNS cancer												
SF-295	4.4	4.5	<4	<4	4.4	4.6	<4	4.4	5.2	4.4	4.6	7.2
SF-539	4.7	4.6	<4	<4	4.5	4.7	<4	4.7	4.5	4.4	4.70	7.4
SNB-75	4.9	4.6	4.6	<4	5.2	4.7	4.2	4.7	4.8	5.3	4.7	6.1
Melanoma												
LOX IMVI	<4	4.2	<4	<4	<4	4.4	<4	5.2	5.8 (5.5,[c] 5.2[e])	<4	4.0	8.0 (4.9)[c]
SK-MEL-5	4.4	4.5	4.2	<4	<4	4.4	<4	4.6	5.5	<4	4.4	8.0
UACC-62	4.4	4.6	<4	<4	4.3	4.6	<4	<4	nt	<4	4.1	8.0
Renal cancer												
786-0	4.6	4.8	<4	<4	4.6	4.7	<4	4.6	5.2	4.3	4.7	7.7
CAKI-1	4.4	4.8	<4	<4	<4	4.6	<4	5.3	5.5	<4	4.6	7.4
RXF 393	nt	nt	nt	<4	nt	4.5	<4	4.8	5.5	nt	4.6	6.1
UO-31	4.4	4.7	<4	<4	<4	4.6	<4	4.4	4.4	<4	4.7	6.7
Prostate cancer												
PC-3	4.4	4.8	<4	<4	<4	4.2	<4	4.3	4.2	<4	4.5	7.5
DU-145	5.8	4.2	<4	<4	nt	4.5	<4	4.5	4.9	<4	4.4	8.0
Breast cancer												
HS 578T	4.5	4.1	<4	<4	4.5	4.8	<4	4.8	4.7	4.4	4.6	6.8
TD-47D	4.5	nt	4.3	<4	<4	4.6	<4	4.5	5.2	<4	4.7	4.3
MG_MID[f]	4.43	4.50	4.13	4.17	4.13	4.55	4.05	4.50	4.88	4.09	4.37	7.00

[a] Values are reported as pGI_{50}, the −log of molar concentration of the compound required to cause 50% inhibition of net cell growth.
[b] http://dtp.nci.nih.gov/dtpstandard/dwindex/index.jsp.
[c] pTGI, the −log of molar concentration of the compound resulting in total inhibition of net cell growth.
[d] nt, not tested.
[e] pLC_{50}, the −log of molar concentration of the compound required to cause 50% net cell death.
[f] MG_MID (mean graph midpoint) is the averaged activity parameter over all cell lines.

Among imidazolone derivatives, compound **5** shows moderate activity against the full NCI 60 cell panel, with a MG-MID value of 4.43. However, **5** exhibits high selectivity against the DU145 prostate cancer cell line (pGI_{50} = 5.8). The 4-chlorophenyl analogue **7** also retains moderate activity in the full NCI 60 cell panel (MG-MID = 4.50), but it shows nanomolar selective inhibitory potency (pGI_{50} > 8) against the CCRF-CEM leukemic cell line. Inversion of pendant aryl rings on the imidazolone core of **7** leads to compound **13** which inhibits in nanomolar concentration the growth of HL-60 (TB) (pGI_{50} = 6.4), MOLT-4 (pGI_{50} = 7.7), and SR (pGI_{50} = 7.5) leukemic cell lines. These are very good results as compared to pGI_{50} values of reference compound CA-4 (Table 1). Replacement of 4-chlorophenyl of **7** with a 4-methoxyphenyl gives the inactive compound **8**. While, the lack of 5-methoxy group in trimethoxyphenyl ring of **8** affords imidazolone **11** that selectively inhibited in sub-micromolar concentrations the growth of leukemic SR cell line at GI_{50} (pGI_{50} = 7.0) and TGI (pTGI = 6.2) levels. This pTGI value as well as those of compounds **13** and **22** (4.4 and 4.8, respectively) are better than that of CA-4 (4.1) (Table 1).

In the series of imidazole-2-thione analogues, compound **32**, which retains the 3,4,5-trimethoxyphenyl group at C-4, shows good potency and selectivity against the CCRF-CEM cell line (pGI_{50} = 6.2) of leukemia sub-panel. Imidazolethione **32** shows a clear improvement of growth inhibitory activity compared to the imidazolone analogue **16**. Lack of 5-methoxy group in trimethoxyphenyl ring of **32** gives compound **35** and results in diminished inhibitory potency. In contrast, replacement of 3-chloro-4-methoxyphenyl of **35** with a 4-chlorophenyl ring gives the analogue **33** and results in remarkable enhancement of antiproliferative activity. As a result, **33** exhibits the best MG_MID value (4.88), with inhibitory potency in low micromolar values against 27 cell lines, being NSCLC HOP-92 the most sensitive (pGI_{50} = 6.5, pTGI = 5.1).

At present, a molecular target responsible for the observed antiproliferative activity of this new series of compounds has not be identified, and a reasonable explanation of SAR described above is not yet possible. Among synthesized compounds, imidazolones **7**, **13**, and imidazolethiones **31**, **32**, bearing a trimethoxyphenyl group, were the most potent and selective in the in vitro assay. Because a trimethoxyphenyl group is considered a structural feature typical for inhibitors of tubulin polymerization,[19] at least for these analogues an antimitotic mechanism of action could be postulated.

Thus, compounds **7**, **13**, and **32** are now submitted to further biological studies, and the relative possible results will be disclosed in due course.

In summary, herein reported preliminary results confirm the validity of our approach providing practical access to imidazolone-based antitumor agents. The reported methods of synthesis have general applicability, so that a large series of compounds would be prepared to extend SAR. Compounds bearing a 3,4,5-trimethoxyphenyl ring linked to either N-1 or C-4 position of imidazole core show the most interesting profile of cytotoxicity with preferential activity against cell lines of the leukemia sub-panel, in some cases with GI_{50} values in nanomolar concentrations. In contrast, the imidazole-2-thione **33**, bearing a 3,4-dimethoxyphenyl group at C-4 position, shows expanded activity spectrum with GI_{50} values in micromolar concentrations. Moreover, several derivatives have been found to be more cytotoxic than CA-4.

Acknowledgments

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15. *General procedure for synthesis of 1*, *4-diaryl-1H-imidazol-2(3H)-ones* ***5–22***. A mixture of **4** (1 mmol) and potassium cyanate (1.2 g, 15 mmol) in acetic acid (2 mL) was stirred for 1 h at 60–65 °C. After cooling, water (20 mL) was added. The insoluble product was filtered off and washed with water, then with cold methanol, to give **5–22** in 56–92% yields. Compound **7**: yield 81%; mp 186–188 °C (EtOH); IR 3142, 1690, 1597 cm^{1};^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 3.94 (s, 6H), 7.25 (s, 2H Ar), 7.59 (d, J = 8.5 Hz, 2H, Ar), 7.72 (m, 2H, Ar + 1H, imidazolic), 11.21 (broad, 1H, NH).
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17. *General procedure for synthesis of 1*,*4-diaryl-1H-imidazole-2(3H)-thiones* ***23–37***. A mixture of **4** (1 mmol) and ammonium thiocyanate (146 mg, 1.5 mmol) in 10% hydrochloric acid (10 mL) was refluxed for 1.5 h. After cooling, the insoluble product was filtered off and washed with water, then with cold MeCN, to give **23–37** in 64–86% yields. Compound **33**: yield 78%; mp 206–208 °C (EtOH/MeCN); IR (Nujol) 3146, 3069, 1624, 1595 cm^{1};^{1}H NMR (300 MHz, DMSO-d_6) δ 3.89 (s, 3H), 3.92 (s, 3H), 7.11 (d, J = 8.5 Hz, 1H Ar), 7.42 (d, J = 8.5 Hz, 1H Ar), 7.49 (s, 1H Ar), 7.71 (d, J = 8.5 Hz, 2H Ar), 7.88 (d, J = 8.5 Hz, 2H Ar), 7.92 (s, 1H, imidazolic), 13.01 (broad, 1H, NH).
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