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Synthesis, biological evaluation and molecular docking studies of 2-amino-3,4,5-trimethoxyaroylindole derivatives as novel anticancer agents

Vijay K. Patel, Harish Rajak *

Medicinal Chemistry Research Laboratory, SLT Institute of Pharmaceutical Sciences, Guru Ghasidas University, Bilaspur 495 009, C.G., India

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ABSTRACT

A series of novel 2-amino-3,4,5 trimethoxyaroylindole derivatives was synthesized and evaluated against selected human cancer cell lines of breast (MCF-7) and colon (HT-29). Introduction of an amino group at the C-2 position on ring A of 3,4,5-trimethoxyaroylindole derivatives resulted in novel compounds, i.e., 2-amino-3,4,5-trimethoxyaroylindole derivatives exhibiting excellent cytotoxic activity against human cancer cell lines. Substitution with methoxy group at R^6 in 2-amino-3,4,5-trimethoxyaroylindole **5d** exhibited excellent cytotoxic activity against MCF-7 (0.013 μM) and colon HT-29 (0.143 μM) indicating slightly higher potency than Combretastatin A-4. Molecular modeling studies of 2-amino-3,4,5-trimethoxyaroylindole derivatives have similar structural alignment as colchicine in protein (PDB code: 1SA0) and exhibited hydrogen bond interaction between *para* position of 3,4,5-trimethoxyphenyl ring with CYS 241 and N–H molecule of indole ring with Val 315 of receptor molecule.

Microtubules has been identified as an attractive and well established molecular targets for anticancer therapy because microtubule influences the crucial processes of cell, such as division, motility, shape maintenance and intracellular transport.[1,2] Combretastatin A-4 (CA-4) is a low molecular weight compound that binds to colchicine binding site causing impediment with microtubule assembly by prevention of tubulin polymerization.[3,4] A number of CA-4 analogues such as CA-4P, EPC2407 (Crolibulin), AVE8062 (ombrabulin), ABT-751 (E7010), OXi4503, T138067, BNC-105P, MPC-6827, etc. are in different phases of clinical trials.[5–7] CA-4 and its analogs have been divided into three major structural elements, i.e., ring A (trimethoxyphenyl ring), ring B (substituted phenyl ring) and the bridgehead linker. The substitution of ethylene bridge of CA-4 with a carbonyl group furnished a benzophenone type CA-4 analogue, named phenstatin. It possess significant anticancer activity in a variety of tumor models, indicating that carbonyl group as linker retain the non-planar character as CA-4.[6] Introduction of an amino group at the C-2 position on ring A of CA-4 and phenstatin analogues exhibited excellent cytotoxic activity in variety of human cell lines (Fig. 1) and tubulin polymerization inhibition. This introduction of amino group causes increased polarity leading to enhancement of the aqueous solubility. Structure–activity relationships (SAR) information indicated that the introduction of an amino group at the C-2 position on ring A of CA-4 and benzophenone analogues plays an important role in maximizing activity.[8–10]

Replacement of ring B to indole derivative prompted to synthesize a series of aroylindole based CA-4 analogs. A number of aroylindole derivatives have been designed and synthesized which exhibit cytotoxic activity on several cancer cell lines due to its excellent antitumor and antivascular activities.[11–16] BPR0L075 (6-methoxy-1*H*-indol-3-yl)(3,4,5-trimethoxyphenyl)methanone have exhibit excellent cytotoxic activity against a panel of cell lines then CA-4 (Fig. 1).[11–13] Introduction of hydroxy group at the C-2 position on ring A of aroylindole derivative exhibits marked antiproliferative activity against KB and MKN45 cells with IC_{50} values of 8.8 and 10.5 nM, respectively, binds strongly to the colchicine binding site and leads to inhibition of tubulin polymerization (Fig. 1).[17] An excellent anticancer activity of aroylindole based CA-4 analogs attracted considerable interest of medicinal chemists in the design and preparation of analogs as novel antitumor agents. Introduction of an amino group at the C-2 position on ring A of 3,4,5-trimethoxyaroylindole derivatives to synthesized 2-amino-3,4,5-trimethoxyaroylindole derivatives which exhibited excellent cytotoxic activity.

The 2-amino-3,4,5-trimethoxyaroylindole derivatives were synthesized by six step reaction sequence, starting with commercially available methyl 3,4,5-trimethoxy benzoate (**1**). The indole substituted 2-nitro-3,4,5-trimethoxyaroylindole derivatives (**4**)

* Corresponding author. Tel.: +91 9827911824; fax: +91 7752260140.
E-mail address: harishdops@yahoo.co.in (H. Rajak).

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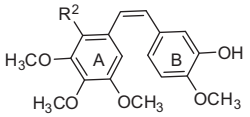
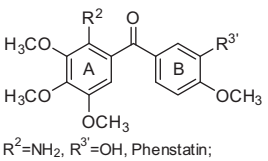
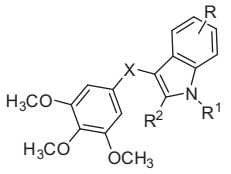


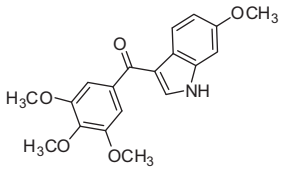
R^2=OH, Combretastatin A-4;
IC_{50}=57nM (HT-29).
R^2=NH_2, 2-amino Combretastatin A-4;
IC_{50} = 36nM (HT-29).



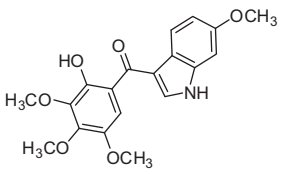
R^2=NH_2, $R^{3'}$=OH, Phenstatin;
IC_{50}=560nM (HT-29).
R^2=NH_2, $R^{3'}$=NH_2, 2-amino Phenstatin derivetive;
IC_{50} = 16nM (HT-29).



Aroylindole derivatives
X=C=O/CH_2;
R=subtitution at different position of indole ring;
R^1=H/CH_3/C_2H_5/CH_2COOH etc;
R^2=H/CH_3/$COOCH_3$/$COOC_2H_5$ etc.

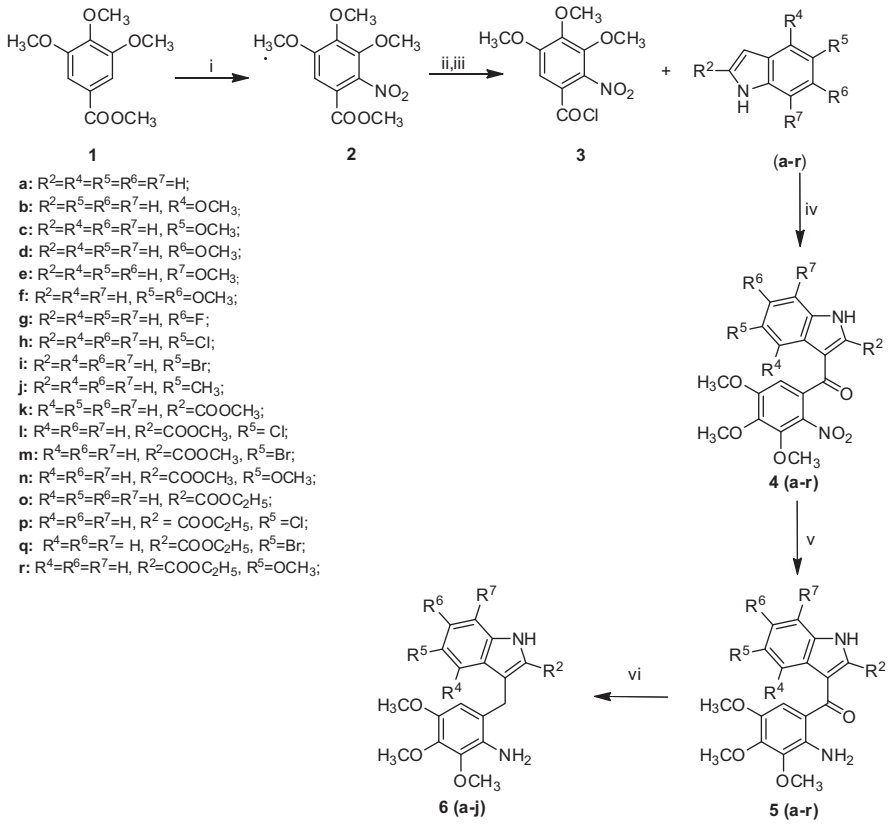


BPR0L075
IC_{50} nM = 7 (MCF-7)/23 (A549)/4 (MESSA)/4 (MKN45)/1 (NUGC)/4 (KB)/7 (H460)/1.1 (HT-29).
CA-4 IC_{50} nM = 8 (MCF-7)/117 (A549)/13 (MESSA)/ 82 (MKN45)/>10000 (NUGC)/6.2 (KB)/17 (H460).



(2-Hydroxy-3,4,5-trimethoxyphenyl)(6-methoxy-1 Hindol-3-yl)methanone
IC_{50} nM = 8.8 (KB)/10.5 (MKN45).
CA-4 IC_{50} nM = 2.5 (KB)/3.2 (MKN45).

Figure 1. Structure and biological activity of Combretastatin A-4, phenstatin and aroylindole derivatives.



1 **2** **3** **(a-r)**

a: R^2=R^4=R^5=R^6=R^7=H;
b: R^2=R^5=R^6=R^7=H, R^4=OCH_3;
c: R^2=R^4=R^6=R^7=H, R^5=OCH_3;
d: R^2=R^4=R^5=R^7=H, R^6=OCH_3;
e: R^2=R^4=R^5=R^6=H, R^7=OCH_3;
f: R^2=R^4=R^7=H, R^5=R^6=OCH_3;
g: R^2=R^4=R^5=R^7=H, R^6=F;
h: R^2=R^4=R^6=R^7=H, R^5=Cl;
i: R^2=R^4=R^6=R^7=H, R^5=Br;
j: R^2=R^4=R^6=R^7=H, R^5=CH_3;
k: R^4=R^5=R^6=R^7=H, R^2=$COOCH_3$;
l: R^4=R^6=R^7=H, R^2=$COOCH_3$, R^5= Cl;
m: R^4=R^6=R^7=H, R^2=$COOCH_3$, R^5=Br;
n: R^4=R^6=R^7=H, R^2=$COOCH_3$, R^5=OCH_3;
o: R^4=R^5=R^6=R^7=H, R^2=$COOC_2H_5$;
p: R^4=R^6=R^7=H, R^2 = $COOC_2H_5$, R^5 =Cl;
q: R^4=R^6=R^7= H, R^2=$COOC_2H_5$, R^5=Br;
r: R^4=R^6=R^7=H, R^2=$COOC_2H_5$, R^5=OCH_3;

4 (a-r) **6 (a-j)** **5 (a-r)**

Scheme 1. Synthesis of 2-amino-3,4,5-trimethoxyaroylindole derivatives. Reagents and conditions: (i) HNO_3, 10–30 °C, stirring for 1–2 h, 26%; (ii) NaOH, EtOH, stirring for 2 h at 45–50 °C, 90%; (iii) CH_2Cl_2, $SOCl_2$, reflux for 1 h at 60 °C; (iv) $AlCl_3$, reflux for 3–5 h, 80–90 °C (Friedel–Craft acylation), 58–73%; (v) Sn, HCl, reflux at 70 °C, 10% K_2CO_3, 42–62%; (vi) $NaBH_4$, EtOH, reflux for 3 h, 32–54%.