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Design, Synthesis, and Anticancer Activity of Amide Derivatives of Structurally Modified Combretastatin-A4

V. Ragha Suma[a,b], R. Sreenivasulu[c], M. Subramanyam[d], and K. Ram Mohan Rao[e]*

[a] *Department of Chemistry, GITAM Institute of Science, Gandhi Institute of Technology and Management, (Deemed to be University), Rushikonda, Visakhapatnam, Andhra Pradesh, 530045 India*
[b] *Department of Chemistry, Government Degree and PG College, Bhadrachalam, Telangana, 507111 India*
[c] *Department of Chemistry, University College of Engineering (Autonomous), Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, 533003 India*
[d] *Department of Chemistry, SR and BGNR Govt. Arts and Science College (Autonomous), Khammam, Telangana, 507002 India*
[e] *Department of Chemistry, GITAM Institute of Technology, Gandhi Institute of Technology and Management, Rushikonda, Visakhapatnam, Andhra Pradesh, 530045 India*
**e-mail: rammohanrao.k@gmail.com*

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Abstract—A new series of amide derivatives of structurally modified combretastatin-A4 **10a**–**10j** are synthesized, and their structures are confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The products are tested for their anticancer activity towards human cancer cell lines, MCF-7 (breast), A-549 (lung), Colo-205 (colon), and A-2780 (ovarian). The compounds **10b**, **10c,** and **10d** demonstrate the most promising activity.

Keywords: combretastatin-A4, cefozopram, 1,2,4-thiadiazoles, anticancer activity
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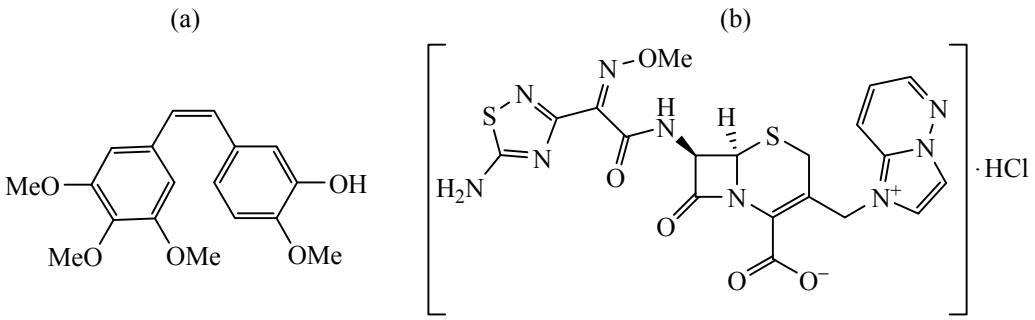
INTRODUCTION

A vast number of heterocyclic derivatives were employed efficiently in anticancer chemotherapy [1–6]. Combretastatin-A4 (**1**), (see the figure) was isolated from South African tree *Combretum caffrumin* [7, 8]. It demonstrated high antitumor activity [9, 10] and acted as vascular disrupting agent (VDA) [11]. Combretastatin-A4 has poor water solubility, high lipophilicity and was easily converted into inactive trans-isomer which made its activity lower [12, 13]. Because of stability problems, many researcher have developed double bond restricted combretastatin derivatives based on triazoles, pyrazoles, thiazoles, furanones, imidazoles, and oxazolones [14-16]. Similarly, 1,2,4-thiadiazole derivatives act as useful units in medicinal chemistry [17] and demonstrate a broad spectrum of biological activities including human leukemia [18], antidiabetic [19], antihypertensive [20], allosteric modulators [21], antibacterial [22], and many more. The FDA approved antibiotic cefozopram (**2**) [23] contains the 1,2,4-thiadiazole unit.

Due to the potent biological activities of combretastin-A4 and 1,2,4-thiadiazole derivatives, we have synthesized a series of structurally modified amide derivatives that combine combretastatin-A4 and 1,2,4-thiadiazole **10a**–**10j**. Their structures were confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The derivatives were tested for their activity against human cancer cell lines.

RESULTS AND DISCUSSION

The first step of synthesis of new amide derivatives of combretastatin-A4 (Scheme 1) was condensation of commercially available trimethoxyphenyl acetonitrile (**3**) with 4-methoxybenzaldehyde (**4**) in presence of TEA which gave the intermediate **5**. Its following cyclization with 4-nitrobenzothioamide (**6**) in presence of $AlCl_3$ led to compound **7**. The nitro group of the precursor **7** was reduced by zinc dust into the corresponding amine **8**. Coupling reaction of the letter compound **8** with a variety of substituted benzoyl chlorides **9a**–**9j** in presence of TEA resulted in formation of the corresponding target compounds **10a**–**10j.**



Structures of (a) Combretastatin-A4 (**1**) and (b) Cefozopram (**2**).

***In vitro* cytotoxicity.** All synthesized derivatives **10a**–**10j** were tested for their anticancer activity against four types of human cancer cell lines, MCF-7 (breast), A-549 (lung), Colo-205 (colon), and A-2780 (ovarian) by the MTT assay method (see the table). Combretatstatin-A4 was used as a positive control. Most of the derivatives demonstrated moderate activity, among those the compounds **10b, 10c, 10d, 10h, 10i,** and **10j** exhibited very high activity. The preliminary analysis of structure-activity relationships (SARs) showed that compound **10b** containing three electro-donating methoxy substituents in positions 3, 4 and 5 on the phenyl ring demonstrated more potent activity than the positive control. The 3,5-dimethoxyphenyl containing analogue **10c** exhibited lower activity than the product **10b.** Along the same line, the product **10d** containing only one methoxy group on the phenyl ring exhibited even lower activity than compounds **10b** and **10c**. The compound **10i** with 4-methyl group demonstrated moderate activity. Interestingly, compound **10j** with the electron-withdrawing 4-cyano group on the phenyl ring exhibited very good activity. The corresponding 3,5-dinitro analogue was characterized by moderate activity.

EXPERIMENTAL

All chemicals were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Reactions progress was monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualized by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra

Anticancer activity of newly synthesized compounds **10a**–**10j**[a]

Compound	IC_{50}, μM			
	A-549[b]	MCF-7[c]	A-375[d]	HT-29[e]
10a	2.870±1.7700	3.450±2.5500	Not active	6.23±3.440
10b	0.011±0.0030	0.023±0.0070	0.120±0.0120	1.78±0.380
10c	0.020±0.0054	0.041±0.0031	0.670±0.0300	1.90±0.440
10d	0.054±0.0043	0.077±0.0090	1.330±0.8200	Not active
10e	2.090±1.8800	2.650±1.5500	7.230±4.7600	10.40±5.790
10f	2.110±1.9300	2.170±1.3400	4.500±3.2200	No active
10g	3.450±2.0900	3.000±1.9900	5.120±3.6800	9.34±5.290
10h	1.440±0.6600	1.200±0.0560	0.330±0.0480	5.13±3.730
10i	0.540±0.0410	1.650±0.990	1.100±0.0320	2.99±1.560
10j	0.060±0.0012	0.013±0.0088	0.098±0.0078	Not active
Combretastatin-A4	0.110±0.0200	0.180±0.0210	0.210±0.0290	0.93±0.034

[a] Each data represents as mean ±S.D values. From three different experiments performed in triplicates. [b] (A-549) human lung cancer cell line. [c] (MCF-7) human breast cancer cell line. [d] (A-375) human melanoma cancer cell line. [e] (HT-29) human colon cancer cell line.