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SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYLISOQUINOLINES AS ANTITUMOR AGENTS

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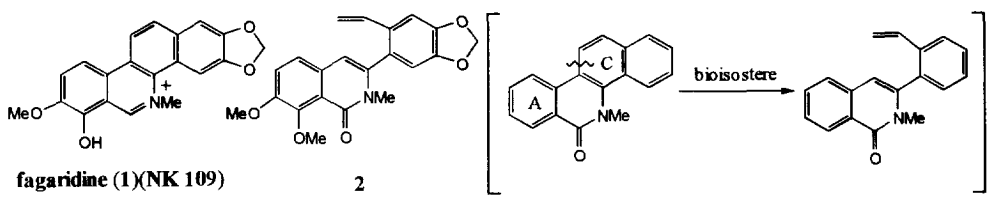
Abstract: To investigate the structure-activity relationship of 7,8-dimethoxy-2-methyl-3-(4,5-methylenedioxy-2-vinylphenyl)isoquinolin-1(2*H*)-one **2**, diverse substituted 3-arylisoquinolines were synthesized and tested *in vitro* antitumor activity against five human tumor cell lines. The results showed a broad antitumor spectrum for a series of 3-arylisoquinolines.

Introduction

With the clinical success of fagaridine **1**,[1, 2] which is a natural phenolic benzo[*c*]phenanthridine alkaloid, considerable attention has been directed towards the synthesis and biological evaluation of related compounds.[3-5] Although synthetic procedures for the preparation of benzo[*c*]phenanthridines have been reported, most of them suffer from certain problems in synthesizing of diverse substituted benzo[*c*]phenanthridines.[6] For this reason, structure-activity relationship studies of these compounds have been limited. During the course of our research in phenolic benzo[*c*]phenanthridines, a strong antitumor agent 7,8-dimethoxy-2-methyl-3-(4,5-methylenedioxy-2-vinylphenyl)-isoquinolin-1(2*H*)-one **2** (IC_{50} = 0.2 nM : SKMEL-2) was discovered.[7, 8] This styrene compound is considered to be a bioisostere of benzo[*c*]phenanthridine *via* its C-C bond cleavage of the aromatic C ring. [9] As an alternative route to the development of new antitumor agents, we decided to do a



fagaridine (1)(NK 109) **2**

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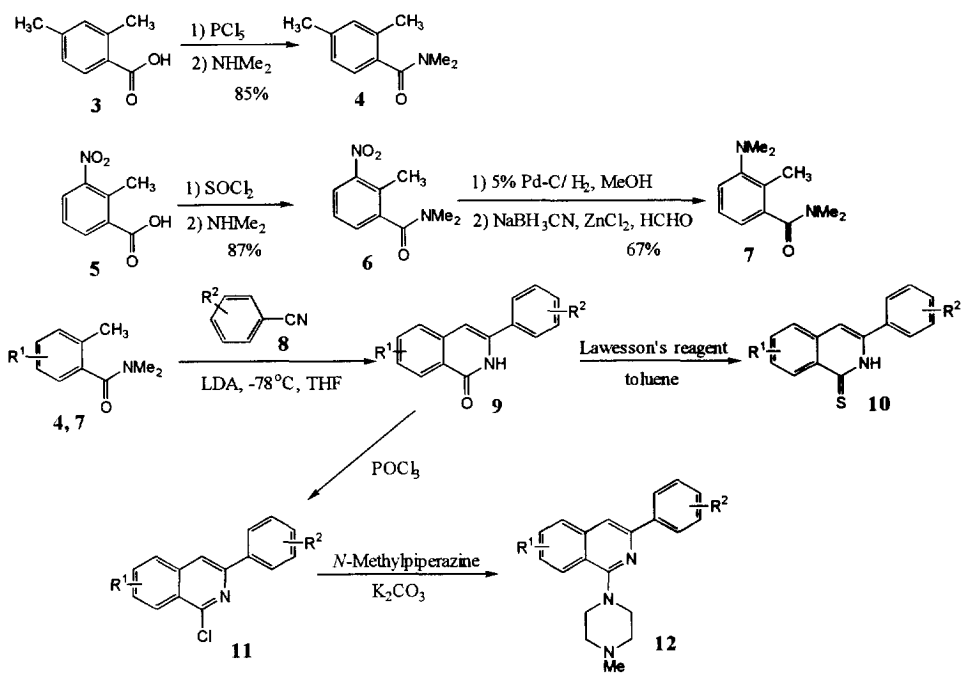
SAR study of 3-arylisoquinolines using the styrene **2** as a lead compound. For the systematic pharmacophore study of **2**, we tried to introduce various substituents (hydrophobic, hydrophilic, electronic) on the two aromatic rings of 3-arylisoquinolines. In order to enhance the water solubility of these compounds, the amide group was designed to be converted to *N*-methyl-piperazinyl group which could retain the hydrogen bonding ability of amide ketone. This paper describes the efficient synthesis of 3-arylisoquinoline derivatives as well as a putative pharmacophore model of these compounds.

Synthesis

3-Nitro-2-methylbenzoic acid **5** was reacted with thionyl chloride, followed by treatment with 40% dimethylamine to afford the amide **6**. The catalytic hydrogenation of **6** and consecutive dimethylation with $NaBH_3CN$ and HCHO yielded the desired amide 7. For the efficient synthesis of 3-arylisoquinolines, we used one pot synthetic pathway developed by Poindexter.[10]



Scheme I. Synthesis of 3-Arylisoquinoline Derivatives

Table I. Cytotoxicity and Synthetic Yield of 3-Arylisoquinolines (μ mole)

Compd	Substitution		Yield	A549	SK-OV-3	SK-MEL-2	XF498	HCT 15
	R1	R2	(%)					
9a	H	H	43	5.75	2.45	2.57	5.89	1.38
9b	H	^{3,4}-OCH_2O	37	na	77.62	25.11	17.78	2.69
9c	H	4-CF_3	40	na	87.28	na	na	na
9d	H	4-Me	57	30.20	13.80	5.01	42.66	7.08
9e	6-Me	H	52	1.32	1.70	1.58	5.13	0.76
9f	6-Me	2-Me	54	5.89	4.27	2.63	30.90	1.99
9g	6-Me	4-Me	55	5.62	4.90	7.76	35.48	11.22
9h	6-Me	4-Cl	47	5.75	6.03	6.31	38.90	11.22
9i	5-NMe_2	H	62	na	na	na	na	na
9j	5-NMe_2	4-Me	65	na	na	na	na	na
9k	5-NMe_2	4-Br	62	na	na	na	na	na
9l	5-NMe_2	4-OMe	53	na	na	na	na	na
10a	H	H	78	na	na	na	na	na
10b	H	4-OMe	82	na	na	na	83.18	na
10c	6-Me	H	54	10.96	56.23	25.12	41.89	75.86
10d	6-Me	H	67	8.51	34.67	19.50	19.05	9.12
12a	H	H	95	25.12	22.38	11.75	37.15	18.62
12b	6-Me	4-OMe	88	7.41	7.94	3.71	9.33	7.41
12c	6-Me	4-Cl	78	3.19	5.75	2.40	6.03	4.07
12d	6-Me	4-Me	72	7.24	7.08	2.40	8.32	4.47
12e	6-Me	2-Me	81	7.59	5.13	3.38	77.62	6.61
12f	5-NMe_2	4-Cl	85	7.45	7.56	4.30	7.98	7.30
12g	5-NMe_2	4-OMe	57	1.82	13.18	3.98	6.17	10.72
12h	5-NMe_2	H	58	10.00	11.22	7.08	19.95	9.55
1	Fagaridine (NK 109)			1.02	1.35	2.75	1.12	1.12

na represents not active (> 100 μmole)

Tumor cell lines : A 549 (human lung), SKOV-3 (human ovarian), SK-MEL-2 (human melanoma), HCT 15 (human colon), XF 498 (human CNS)

o-Toluamides **4**,**7** were reacted with two equivalent of LDA at 0°C to form anions which were then treated with benzonitriles **8** to afford the corresponding amides **9**. The thioketones **10** were prepared with Lawesson's reagent in refluxing toluene.[11] The amides **9** were reacted with $POCl_3$ to give chloroimines **11** in good yield which were then transformed to 1-(4-methylpiperazinyl)isoquinolines **12** as shown in Scheme I.

Biological Discussion

The cytotoxicity experiment of the synthesized compounds [12] were performed *in vitro* against five human cell lines such as A 549 (lung), SKOV-3 (ovarian), SK-MEL-2 (melanoma), XF 498 (CNS) and HCT 15 (colon) using sulforhodamine B (SRB) assay.[13,14] Unsubstituted amides **9a** exhibited 5 to 35 times stronger activity than the amides of substituted B ring **9b-9d** in SK-OV-3 cell line. 6-Methyl amide **9e** displayed a potency increase, 4 times stronger than the unsubstituted compounds **9a** in A-549 cell line. This result indicates that the methyl group on A ring seemed to significantly affect the level of activity. On the other hand, the dimethylamino compounds **9i-9l** did not show much activity. When we replaced the amide carbonyl with thioketone, the activity decreased dramatically. However, the piperazinyl substituted compounds **12a-12h** displayed broad antitumor activity against most cell lines regardless of the substitution on A ring or B ring. To determine the reason for this activity difference between amide and thioamide compounds, we calculated the atomic charge which is important for hydrogen bonding ability of amide carbonyl (-0.274), thioketone (-0.065) and piperazinyl nitrogen (-0.256) using Gasteiger method.[15] The results strongly indicate that these compounds have three important binding sites for the receptor, two hydrophobic regions of aromatic A and B ring and one hydrogen bonding region. Accordingly, a pharmacophore model of 3-arylisoquinolines was postulated as shown in figure I.[16] Compounds **12a**, a representative water soluble piperazinyl analogue, was tested *in vivo* assay using BDF1 mouse (P 388 leukemia) and resulted in 160 T/C %. [17]

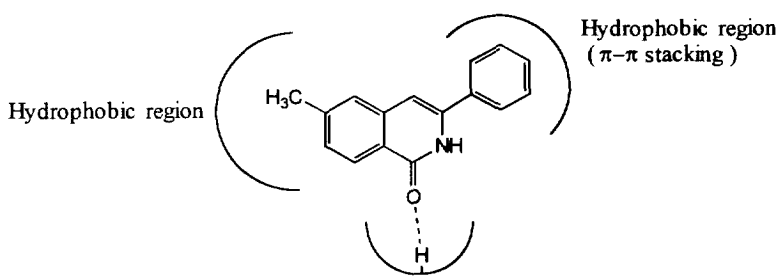


Figure I. Schematic Representation of Proposed Pharmacophore Model of 3-Arylisoquinolines

In summary, novel antitumor 3-arylisoquinoline derivatives were developed as plausible antitumor agents, which showed comparable activity as fagaridine (**NK 109**, **1**) [18] but could not exceed the lead compound **2**. A study of the function of vinyl moiety and other substitutions on **2** is in progress.

Acknowledgement

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12. All Synthesized compounds were fully characterized by spectroscopy. Selected data for key compounds : Compound **9g** : mp 250-251℃, ^{1}H-NMR (300MHz) : 10.05 (1H, s, NH), 8.28 (1H, d, *J*=8.4Hz, C_8-H), 7.62 (2H, d, *J*=8.0Hz, aromatic), 7.31 (2H, d, *J*=8.0Hz, aromatic), 7.36-7.26 (2H, m, aromatic), 6.69 (1H, s, C_4-H), 2.49, 2.42 (each 3H, s, CH_3). IR (KBr) (cm^{-1}): 1650 (amide). MS, m/z (%): 249 (M^+, 100), 219 (33), 169 (36), 149 (69). **12f**: oil. ^{1}H-NMR (300MHz): 8.13 (2H, d, *J*=8.7Hz, aromatic), 8.03 (1H, s, C_4-H), 7.70 (1H, d, *J*=8.1Hz, C_8-H), 7.42 (2H, d, *J*=8.7Hz, aromatic), 7.39-7.33 (1H, m, C_7-H), 7.12 (1H, d, *J*=7.5Hz, C_6-H), 3.58 (4H, t, *J*=4.5Hz, -N-$\underline{CH_2}$-CH_2-N-Me), 2.91 (6H, s, NMe_2), 2.73 (4H, t, *J*=4.5Hz, -N-CH_2-$\underline{CH_2}$-N-Me), 2.43 (3H, s, NMe). MS, m/z (%) : 381 (M^+, 15), 313 (27), 310 (75), 297 (100).
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15. Charge calculation was performed using Gasteiger method in the Sybyl program (Version 6.3) supplied by Tripos Associates, 1699 South Hanley Road, Suite 303, St. Louis, Missouri 63144, USA.
16. The result of comparative molecular field analysis (CoMFA), three dimensional quantitative structure-activity relationship study, of 3-arylisoquinolines indicated that the above pharamcophore model showed quite a good correlation with the contour map derived from this computational analysis. This CoMFA result will be reported soon elsewhere.
17. For testing *in vivo* assay of the representative compound **12a**, female BDF1 mice were inoculated IP with P 388 leukemia cells (10 controls and 6 animals in each test group), and the test compound was injected intraperitoneally as 0.2 mL solutions (PBS) at 1, 3, 5, 7 and 9 days after leukemia inoculation. T/C is expressed as the ratio of the median survival time of treated animals to the median control time multiplied by 100.
18. The mode of action of fagaridine (**NK 109, 1**) developed in Nippon Kayaku in Japan in known as topoisomerase II inhibitor. The synthesized 3-arylisoquinolines are under estimation of topoisomerase inhibition activity.