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SYNTHESIS OF RUTAECARPINE AND CYTOTOXIC ANALOGUES

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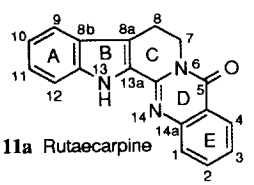
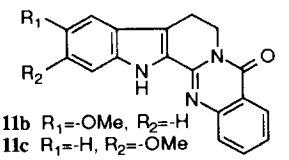
Abstract: Analogues of rutaecarpine, a quinazolinocarboline alkaloid, were synthesized by structurally modifying the A-ring to yield 10-methoxy (**11b**), 11-methoxy (**11c**), and 10,11-methylenedioxy (**11d**) derivatives. Analogues **11c,d** displayed activity superior to rutaecarpine when evaluated against several tumor cell lines *in vitro*.

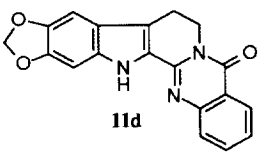
Rutaecarpine **11a**, which has been isolated from the fruits of *Evodia rutaecarpa*,[1] and its naturally occurring derivatives belonging to the class quinazolinocarboline alkaloids[2] are known to possess cardiotonic[3] and analgesic properties[4] and have been used for the treatment of gastro-intestinal disorders and migraine. No published data are available concerning the cytotoxicity screening of the rutaecarpine analogues. In a continuing program to develop natural products with antitumor activity, our laboratory has been engaged in the design and synthesis of rutaecarpine analogues. The original investigations were focused on how substituent changes in the A-ring of the molecule would affect antitumor activity. Assay results from the NCI's *in vitro* primary cytotoxicity screen were used to facilitate the discovery and design of new, selective, cytotoxic leads with improved antitumor activities compared to rutaecarpine for further antitumor mechanistic investigations. In this paper, we will present the synthesis and cytotoxic evaluation of rutaecarpine (**11a**) and a series of analogues (**11b-d**) with alkoxy groups at the C-10 and C-11 positions.



11a Rutaecarpine



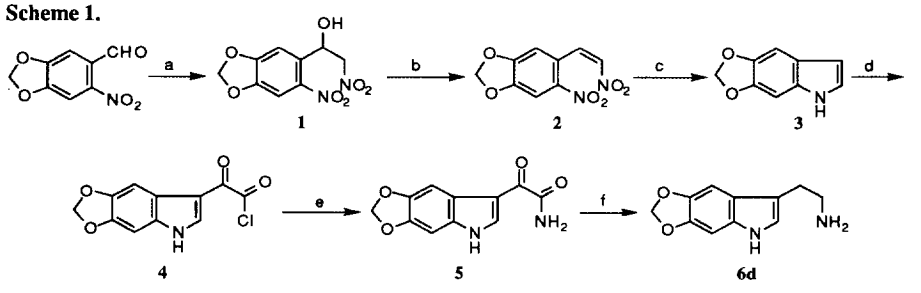
11b R_1=-OMe, R_2=-H
11c R_1=-H, R_2=-OMe



11d

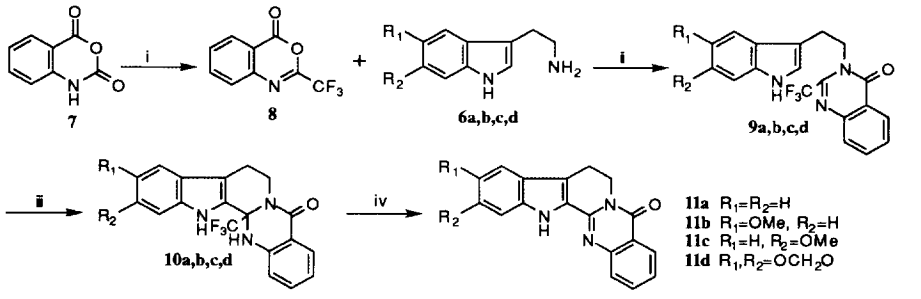
The synthesis of 10,11-methylenedioxyrutaecarpine **11d** is illustrative of the methods used and is shown in Scheme 1 and 2. The intermediate 5,6-methylenedioxytryptamine **6d** was initially synthesized as outlined in Scheme 1. First, the nitroalcohol **1** (84%) was obtained as a slowly crystallizing oil through condensation of 6-nitropiperonal with nitromethane in the presence of sodium in ethanol. Compound **1** was treated directly with sodium acetate and acetic anhydride to give the dinitro-4,5-methylenedioxstyrol **2**. Catalytic reduction[5] of **2** with palladium on carbon in ethyl acetate-ethanol in the presence of six molar equivalents of acetic acid gave the 5,6-methylenedioxyindole **3** (94%). Reacting **3** with oxalyl chloride in ether gave the corresponding 5,6-methylenedioxyindolylglyoxalyl chloride **4**, which was treated without further purification with ammonium hydroxide to give the more stable 5,6-methylenedioxy-3-indolylglyoxamide **5**. The 5,6-methylenedioxytryptamine **6d** (47%)[6] was obtained by reduction of **5** with lithium aluminum hydride in THF.[7]

Scheme 1.



Reagents: (a) (i) $MeNO_2$, Na, EtOH. (ii) c-HCl, H_2O; (b) Ac_2O, NaOAc; (c) 10% Pd/C, H_2, G-AcOH, EtOH, EtOAc; (d) $(COCl)_2$, Et_2O; (e) 25% NH_4OH; (f) $LiAH_4$, THF.

Scheme 2.



Reagents: (i) $(CF_3CO)_2O$, Py, 25°, 15'; (ii) 115°, 30'; (iii) HCl, AcOH; (iv) KOH, H_2O, EtOH.

Rutaecarpine **11a** and its analogues **11b-d**, were synthesized as shown in Scheme 2. The isatonic anhydride **7** was dissolved in pyridine containing trifluoroacetic anhydride to give 2-(trifluoromethyl)-4-oxazinone **8**. Compounds **11a-d** were then prepared according to the Bergman[8,9] procedure. Combination of tryptamines **6a-d** with **8** gave **9a-d**; reflux under acidic conditions (HCl-AcOH) for 30 min. then gave **10a-d**. Elimination of CF_3H was accomplished by treating **10a-d** with alcoholic KOH to form the rutaecarpine analogues **11a-d**, respectively. Their proposed structures were satisfactorily confirmed by detailed NMR analysis as shown in Table 1.

Table 1. ^1H NMR data of **11a-d**.

	H-1	H-2	H-3	H-4	H-7	H-8	H-9	H-10	H-11	H-12	N-H	-OMe	$-OCH_2O$
11a	7.66 d	7.76 t	7.42 t	8.12 d	4.42 t	3.13 t	7.58 d	7.05 dd	7.24 dd	7.48 d	11.76	—	—
11b	7.67 d	7.79 t	7.44 t	8.12 d	4.42 t	3.13 t	7.10 d	—	6.92 q	7.34 d	11.71	3.77	—
11c	7.66 d	7.78 t	7.43 t	8.11 d	4.41 t	3.12 t	7.50 d	6.75 q	—	6.91 d	11.71	3.79	—
11d	7.63 d	7.77 t	7.42 t	8.10 d	4.39 t	3.08 t	7.10	—	—	6.91	11.70	—	6.00

Chemical shifts (δ) in DMSO-d_6 at 200 MHz (ppm from TMS).

Compounds **11a-d** were screened in the NCI *in vitro* human tumor cell line panel,[10,11] which uses approximately 45 different cell lines derived from nine cancer types. The results in Table 2 are the GI_{50} values (μM) found in five tumor subpanels, leukemia (CCRF-CEM), non-small cell lung cancer (A549/ATCC and NCI-11460), renal cancer (786-0), ovarian cancer (OVCAR-4), and breast cancer (HS-578T).

The 11-methoxyrutaecarpine analogue (**11c**)[12] showed selective cytotoxicity against the lung and renal cancer subpanel, while the 10,11-methylenedioxy analogue (**11d**) showed selective cytotoxicity for the ovarian cancer subpanel. A portion of the screening data available for these derivatives is shown in Table 2.

Table 2. Cytotoxicity of rutaecarpine analogues (GI_{50} Values, μM)[a].

	CCRF-CEM	A549/ATCC	NCI-H460	OVCAR-4	786-0	HS-578T
11a	18.9	14.5	—	18.9	—	22.6
11b	>25.0	>25.0	>25.0	>25.0	>25.0	>25.0
11c	>25.0	0.75	1.38	>25.0	0.31	1.59
11d	>25.0	>25.0	1.55	1.50	1.08	5.05

[a] The cytotoxicity GI_{50} values are the concentrations corresponding to 50% growth inhibition, and they are the averages of at least two determinations.

Both of these analogues **11c,d** showed higher potency than rutaecarpine (**11a**) itself. On the other hand, 10-methoxyrutaecarpine (**11b**)[13] showed no activity. It is interesting to note that substitution with alkoxy groups at the 11- or the 10,11- positions of the A-ring, as in **11c** and **11d** significantly increased the *in vitro* selective cytotoxicity, but an alkoxy group at the 10-position, as in **11b**, diminished activity and sensitivity to these tumor cell lines.

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