Synthesis and COX Inhibitory Activities of Rutaecarpine Derivatives

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A series of substituted rutaecarpines were prepared by employing Fischer indole synthesis as key step and their inhibitory activities on COX-1 and 2 as well as selectivity on COX-2 were evaluated. The compounds with a methanesulfonyl and a bromo group at C10 showed promising inhibitory activity (IC_{50} = 0.27, 0.35 μM, respectively) with selectivity.

Key Words : Rutaecarpine, COX-2 inhibitor, Antiinflammatory activity, Indoloquinazoline alkaloid

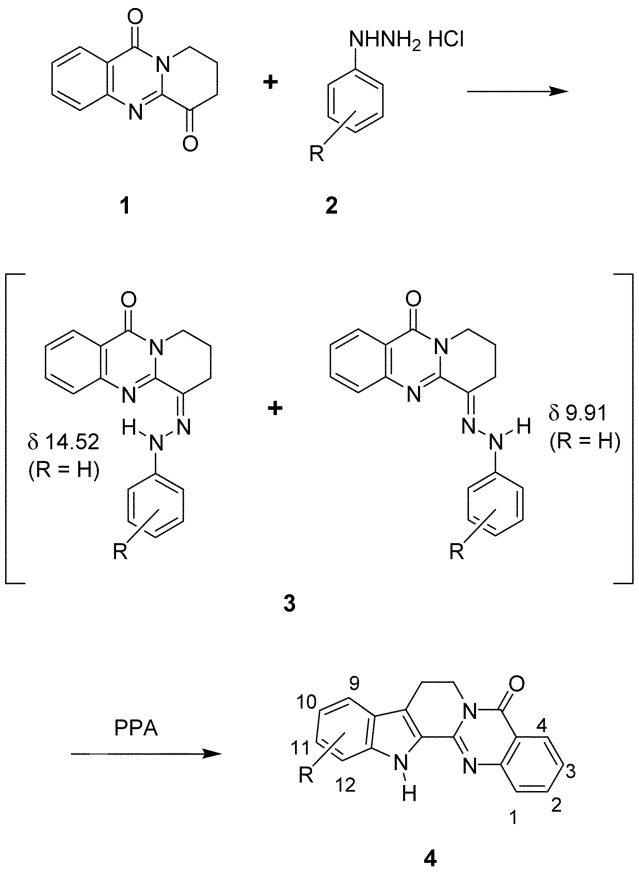
Introduction

Rutaecarpine is a major indoloquinazoline alkaloid isolated from Rutaceous plants[1] such as *Evodia rutaecarpa* and *Evodia officinalis*, which have long been used for the treatment inflammation-related symptoms in the traditional oriental medicinal practice.[2] Recent studies revealed that such an anti-inflammatory activity stemmed from its components rutaecarpine (structure **4** in which R = H), which showed potent and selective inhibitory activity against COX-2.[3] Addition to anti-inflammatory activity, the vaso-relaxing,[4] analgesic,[5] antiplatelet,[6] antianoxic,[7] and cytotoxic activities[8] were reported for rutaecarpine. Such intriguing activities led to the development of efficient methods for total synthesis.[9] The preparation of its derivatives specially on the indole ring, however, is somewhat limited presumably due to the lack of general applicability of the synthetic method.[8,10]

As a part of our interest in safer anti-inflammatory drugs,[11] we herein described preparation of a variety of rutaecarpine derivatives and their inhibitory activities on COX-1 and 2.

Results and Discussion

Chemistry. The synthesis of rutaecarpine derivatives was straightforward as shown. The prerequisite 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazoline-6,11-dione (**1**) was prepared by previously reported method.[9f] The diketone **1** was reacted with a series of substituted phenylhydrazine or its HCl salt to afford the corresponding hydrazones **2** in over 67% yields. Most of the cases, the hydrazones were soluble enough to get good ^{1}H NMR spectra in either DMSO-d_6 or CD_3OD. In some cases of hydrazones, the presence of two isomers through C=N bond were observed in ^{1}H NMR spectra, which could be readily assignable due to the proton resonances of N-H's. The resonance of H of Z-isomer's were more deshielded (approximately $\Delta\delta$ 0.5 ppm) by hydrogen bonding to N1 of the quinazolinone ring to show a singlet in the range of δ 14.88-11.52 in DMSO-d_6. These two isomers, however, were not separated but instead subjected to next step in most of the compounds. Fischer's indole synthetic method was applied to hydrazones **3** afforded the desired derivatives of rutaecarpine (**4**) series in the yields of 65-95%.



This method has advantages that 9-, 10-, 11- and 12-substituted rutaecarpines can be prepared from three isomeric hydrazines: The 2- and 4-substituted phenylhydrazines afforded 12- and 10-substituted rutaecarpines, respectively, while 3-substituted phenylhydrazines two regioisomers, 9- and 11-substituted. Two regioisomers from 3-substituted phenylhydrazines were separable in most of the cases and could be readily assigned by comparing ^{1}H NMR in which 11-substituted isomer showed a doublet for H12

Table 1. Inhibitory Activities of Rutaecarpine Derivatives on COX

Compound (R)	Inhibitory Activity[a]		Selectivity[b]	Compound (R)	Inhibitory Activity		Selectivity
	COX-1	COX-2			COX-1	COX-2	
4a (H)	8.7	0.28	31	**4da/4dc**[c]	11.6	6.5	2
4ba (9-F)	>50	17.8	–	**4db**(10-Br)	10.6	0.27	39
4bb (10-F)	11.2	2.35	5	**4dd**(12-Br)	16.6	1.25	13
4bc (11-F)	32.6	10.2	3	**4eb**[d]	21.6	0.35	62
4bd (12-F)	21.6	5.6	4	**4ed**[d]	25.6	2.22	12
4ca (9-Cl)	>50	34.6	–	**4fa/4fc**[c]	>50	>50	–
4cb (10-Cl)	>50	8.2	>6	**4fb**(10-Me)	>50	23.8	–
4cc (11-Cl)	>50	>50	–	**4fd**(12-Me)	>50	35.5	–
4cd (12-Cl)	34.2	8.7	4	NS-398	1.67	<0.002	>8,300

[a]Results were mean values of duplicated experiments and shown as IC_{50} (μM). [b]Values calculated by IC_{50} (COX-1)/IC_{50} (COX-2). [c]A mixture of 9- and 11-isomer. [d]**4eb** (10-CH_3SO_2), **4ed** (12-CH_3SO_2).

with characteristic *meta* coupling constant (J = 2.3 Hz). Most of the rutaecarpine derivatives showed resonances in the range of δ 8.18-8.10 for H4, while H12 resonanced in the range of δ 7.73-7.25. With most electronegative halogen as a substituent, all proton resonances were down-field shifted. The effects were most significant for the resonances of H12 which were 0.50 and 0.25 ppm down-field shifted compared to electron donating CH_3 and parent rutaecarpine, respectively.

Biology. The compounds prepared were evaluated their inhibitory activities against cyclooxygenase-1 and 2 (COX-1 and COX-2) by employing previously reported method,[3] and are summarized in Table 1.

Compounds with a Br and CH_3SO_2 group at C10 and C12 showed similar inhibitory activities on COX-2 comparable to parent rutaecartpine with improved selectivity on COX-2. Compounds with a susbtituent at C10 or C12 showed stronger selectivity on COX-2. Compound with a CH_3SO_2 group at C10 showed best selectivity by decreasing activity on COX-1 while 10-bromorutaecarpine compound showed strongest inhibitory activity on COX-2 (IC_{50} = 0.27 μM).

It is worthy to noting that the introduction of a substituent on benzene ring of 4(3*H*)-quinazolinone moiety resulted in increasing cytotoxcity (not described herein), which does not allow evaluation of inhibitory activity on COX-1 and 2. Studies on cytotoxicity of rutaecarpine derivatives will be due in the near future.

In conclusion, a series of substituted rutaecarpines were prepared by employing Fischer indole synthesis as key step. Inhibitory activities of the compounds on COX-1 and 2 were evaluated. The compounds with a methanesulfonyl and a bromo group at C10 showed promising inhibitory activity (IC_{50} = 0.27, 0.35 μM, respectively) with selectivity (62 and 35 times more selective on COX-2, respectively).

Experimental Section

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz for ^{1}H NMR and 62.5 MHz for ^{13}C NMR and are reported as ppm from the internal standard TMS. Chemicals and solvents were commercial reagent grade and used without further purification. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer. The starting 2- and 4-methanesulfonylphenylhydrazine hydrochlorides were prepared by previously reported method.[12]

(i) Hydrazones

6-(2-Fluorophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3ba). Into a solution of 200 mg (0.93 mmol) of **1** in 20 mL of 95% EtOH was added a solution of 163 mg (0.97 mmol) of 2-fluorophenylhydrazine·HCl in 10 mL of 95% EtOH. The resulting mixture was stirred for 15 h at room temperature to give 231 mg (77%) of pale yellow needles which was recrystallized from CH_2Cl_2: mp 197-198 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 14.87 (s, NH), 8.24 (d, J = 7.9 Hz, 1H), 7.77-7.60 (m, 3H), 7.46 (ddd, J = 8.0, 6.7, 1.5 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.04 (dd, J = 8.3, 1.3 Hz, 1H), 6.90-6.81 (m, 1H), 4.09 (t, J = 5.9 Hz, 2H), 2.87 (t, J = 6.2 Hz, 2H), 2.15 (quintet, J = 6.2 Hz, 2H).

6-(3-Fluorophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3bb). The same procedure described above for **3ba** with 200 mg (0.93 mmol) of **1** and 205 mg (1.22 mmol) of 3-fluorophenylhydrazine·HCl to afford 287 mg (96%) of pale yellow needles: mp 192 °C.

6-(4-Fluorophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3bc). The same procedure described above for **3ba** with 160 mg (0.75 mmol) of **1** and 210 mg (1.25 mmol) of 4-fluorophenylhydrazine·HCl to afford 200 mg (83%) of pale yellow needles: mp 227 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 14.68 (s, NH), 8.31 (dd, J = 7.5, 0.8 Hz, H5/8), 7.83 (td, J = 7.7, 0.9 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.29-7.22 (m, 2H), 7.06 (overlapped t, J = 8.8 Hz, 2H), 4.14 (t, J = 6.0 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 2.16 (quintet, J = 6.2 Hz, 2H).

6-(2-Chlorophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3ca). The same procedure described above for **3ba** with 210 mg (0.98 mmol) of **1** and 180 mg (1.01 mmol) of 2-chlorophenylhydrazine·HCl to afford 270 mg (81%) of pale yellow needles: mp 199 °C. ^{1}H

NMR (250 MHz, $CDCl_3$) δ 11.68 (s, NH), 8.23 (dd, J = 7.5, 0.9 Hz, H5/8), 7.73 (m, 2H), 7.66 (dd, J = 8.2, 1.5 Hz, 1H), 7.43 (td, J = 7.2, 1.8 Hz, 1H), 7.30 (dd, J = 8.0, 1.3 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 6.84 (td, J = 7.8, 1.3 Hz, 1H), 4.08 (t, J = 5.8 Hz, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.13 (m, 2H).

6-(3-Chlorophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3cb). The same procedure described above for **3ba** with 198 mg (0.93 mmol) of **1** and 167 mg (0.91 mmol) of 3-chlorophenylhydrazine·HCl to afford 272 mg (88%) of pale yellow needles: mp 194 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.63 (s, NH), 8.28 (dd, J = 7.5, 0.9 Hz, H5/8), 8.18 (d, J = 8.0 Hz, 1H), 7.99 (td, J = 7.8, 1.2 Hz, 1H), 7.90 (overlapped d, J = 8.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 2H), 7.36 (overlapped t, J = 9.0 Hz, 2H), 4.12 (t, J = 5.8 Hz, 2H), 2.88 (t, J = 6.3 Hz, 2H), 2.16 (m, 2H).

6-(4-Chlorophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3cc). The same procedure described above for **3ba** with 201 mg (0.94 mmol) of **1** and 166 mg (0.90 mmol) of 4-chlorophenylhydrazine·HCl to afford 146 mg (48%) of pale yellow needles: mp 184 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.47 (s, NH), 8.21-8.17 (m, 2H), 7.97 (td, J = 8.3, 0.9 Hz, 1H), 7.83 (overlapped d, J = 8.8 Hz, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.41 (overlapped t, J = 8.6 Hz, 2H), 3.99 (t, J = 5.8 Hz, 2H), 2.84 (t, J = 6.3 Hz, 2H), 2.14 (m, 2H).

6-(2-Bromophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3da). The same procedure described above for **3ba** with 196 mg (0.91 mmol) of **1** and 204 mg (0.90 mmol) of 2-bromophenylhydrazine·HCl to afford 315 mg (92%) of pale yellow needles: mp 199 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 14.5 (s, NH), 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.83 (td, J = 8.3, 1.5 Hz, 1H), 7.72 (dd, J = 8.2, 1.8 Hz, 1H), 7.56-7.47 (m, 2H), 7.33 (td, J = 8.6, 1.5 Hz, 1H), 6.85 (td, J = 8.0, 1.5 Hz, 1H), 4.16 (t, J = 5.8 Hz, 2H), 2.92 (t, J = 6.3 Hz, 2H), 2.21 (m, 2H).

6-(3-Bromophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3db). The same procedure described above for **3ba** with 200 mg (0.93 mmol) of **1** and 209 mg (0.92 mmol) of 3-bromophenylhydrazine·HCl to afford 259 mg (74%) of pale yellow needles: mp 208 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.34 (s, NH), 8.21 (d, J = 8.0 Hz, 1H), 8.03 (s, H), 7.98 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 4.13 (m, 2H), 2.84 (t, J = 6.2 Hz, 2H), 2.14 (m, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 159.06, 151.64, 144.85, 136.40, 131.27, 129.67, 128.02, 127.29, 125.74, 122.55 (two C's), 120.77, 117.99 two C's), 114.84, 41.56, 23.52, 18.50.

6-(4-Bromophenylhydrazono)-7,8,9,11-tetrahydropyrido [2,1-*b*]quinazoline-11-one (3dc). The same procedure described above for **3ba** with 200 mg (0.94 mmol) of **1** and 209 mg (0.94 mmol) of 4-bromophenylhydrazine·HCl to afford 314 mg (88%) of pale yellow needles: mp 186 °C.

6-(4-Methanesulfonylphenylhydrazono)-7,8,9,11-tera-hydropyrido[2,1-*b*]quinazoline-11-one (3ec). The same procedure described above for **3ba** with 400 mg (1.87 mmol) of **1** and 403 mg (2.61 mmol) of 4-methanesulfonyl-phenylhydrazine·HCl to afford 680 mg (95%) of pale yellow needles as a *E*-isomer (major, 64%): mp 187 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 14.81 (s, NH), 8.28 (dd, J = 8.3, 1.5 Hz, 1H), 7.87-7.75 (m, 4H) 7.47-7.44 (m, 2H), 7.45 (d, J = 7.3 Hz, 1H), 4.23 (t, J = 5.8 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 1.83 (m, 2H). The mother liquid afforded Z-isomer (minor, 31%): mp 200 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 14.88 (s, NH), 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 7.87 (over-lapped d, J = 8.3 Hz, 2H), 7.81 (td, J = 8.3, 1.5 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.53 (td, J = 8.6, 1.5 Hz, 1H), 7.35 (overlapped d, J = 8.0 Hz, 2H), 4.14 (t, J = 5.8 Hz, 2H), 2.91 (t, J = 6.3 Hz, 2H), 2.21 (m, 2H).

6-(2-Tolylhydrazono)-7,8,9,11-tetrahydropyrido[2,1-*b*]-quinazoline-11-one (3fa). The same procedure described above for **3ba** with 184 mg (0.86 mmol) of **1** and 224 mg (1.37 mmol) of 2-tolylhydrazine·HCl to afford 249 mg (91%) of pale yellow needles: mp 207-208 °C: ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.26 (s, NH), 8.20 (d, J = 8.0 Hz, H_5), 8.13 (d, J = 8.5 Hz, H_8), 7.98 (t, J = 7.3 Hz, H_6), 7.68-7.61 (m, 3H), 7.20 (m, 2H), 4.12 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 6.3 Hz, 2H), 2.28 (s, 3H), 2.13 (m, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 159.03, 151.77, 140.87, 138.16, 136.37, 132.90, 130.00, 129.81 (two C's), 127.74, 127.33, 126.88, 120.17, 117.66, 116.01, 41.52, 23.11, 20.71, 18.43.

6-(3-Tolylhydrazono)-7,8,9,11-tetrahydropyrido[2,1-*b*]-quinazoline-11-one (3fb). The same procedure described above for **3ba** with 150 mg (0.70 mmol) of **1** and 157 mg (0.98 mmol) of 3-tolylhydrazine·HCl to afford 194 mg (587) of pale yellow needles: mp 283-286 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 14.37 (s, NH), 8.17 (d, J = 8.0 Hz, H_5), 7.89 (t, J = 7.8 Hz, H_6), 7.70 (d, J = 8.3 Hz, H_8), 7.59-7.52 (m, 2H), 7.20-7.18 (m, 2H), 6.85 (t, J = 7.3 Hz, 1H), 4.02 (t, J = 5.8 Hz, 2H), 2.81 (t, J = 5.8 Hz, 2H), 2.44 (s, 3H), 2.08 (br. s, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 159.64, 152.51, 143.76, 139.33, 138.64, 137.04, 129.81, 128.48, 127.97 (two C's), 125.16, 120.85, 118.31, 117.19, 114.06, 42.24, 23.93, 22.10, 19.07.

6-(4-Tolylhydrazono)-7,8,9,11-tetrahydropyrido[2,1-*b*]-quinazoline-11-one (3fc). The same procedure described above for **3ba** with 108 mg (0.51 mmol) of **1** and 100 mg (0.62 mmol) of 4-tolylhydrazine·HCl to afford 136 mg (84%) of pale yellow needles: mp 185-186 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.35 (s, NH), 8.20 (dd, J = 8.3, 1.5 Hz, H_5 and H_8), 7.99 (td, J = 8.3, 1.5 Hz, H_6), 7.67-7.57 (m, 3H), 7.26 (t, J = 7.8 Hz, H_7), 6.89 (d, J = 8.0 Hz, 1H), 4.12 (t, J = 5.8 Hz, 2H), 2.83 (t, J = 6.3 Hz, 2H), 2.33 (s, 3H), 2.14 (br. s, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 160.63, 147.95, 145.34, 142.00, 135.07, 130.73, 127.56, 127.33, 126.51, 126.20, 121.88, 121.17, 111.82, 43.03, 30.87, 20.90, 17.79.

(ii) Substituted Rutaecarpines

12-Fluororutaecarpine (4bd). A mixture of 0.20 g (0.62 mmol) hydrazone **3ba** with 5 g of polyphosphoric acid in a heavy-walled beaker was heated at 210 °C for 3 h. After cooling, the mixture was made basic with 10% NaOH and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic

layers were washed water, dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a solid material which was recrystallized from ethyl acetate to provide **4bd** as pale yellow needles (0.15 g, 79%): mp 237 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.23 (s, N-H), 8.36 (d, J = 8.2 Hz, H1), 7.98 (t, J = 7.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.48 (overlapped t, J = 7.0 Hz, 2H), 7.12-7.01 (m, 2H), 4.44 (t, J = 6.8 Hz, 2H), 3.17 (t, J = 6.8 Hz, 2H). *Anal.* Calcd for $C_{18}H_{12}FN_3O$: C, 70.81; H, 3.96; N, 13.76. Found: C, 70.78; H, 4.02; N, 13.56.

9-Fluororutaecarpine (4ba) & 11-Fluororutaecarpine (4bc). The same procedure described above for **4bd** was employed with 0.65 (2.01 mmol) of hydrazone **3bb** to yield 0.56 g (92%) of yellow needles whose ^{1}H NMR spectrum showed presence of two isomers in a ratio of 5.4 : 1. The major component had a characteristic singlet at δ 7.73 for H12 which confirmed 11-fluororutaecarpine as a major. Repeated recrystallization from EtOAc : CH_3OH afforded two pure isomers. **9-Fluororutaecarpine (4ba)**: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.38 (s, NH), 8.53 (dd, J = 8.0, 1.3 Hz, 1H), 8.18 (td, J = 8.0, 1.3 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.85 (td, J = 7.5, 0.9 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.34 (td, J = 6.8, 1.2 Hz, 1H), 4.83 (t, J = 6.8 Hz, 2H), 3.55 (t, J = 6.8 Hz, 2H). **11-Fluororutaecarpine (4bc)**: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.28 (s, NH), 8.53 (dd, J = 8.0, 1.3 Hz, 1H), 8.18 (td, J = 8.0, 1.3 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.85 (td, J = 7.5, 0.9 Hz, 1H), 7.73 (s, 1H), 7.34 (td, J = 6.8, 1.2 Hz, 1H), 4.83 (t, J = 6.8 Hz, 2H), 3.55 (t, J = 6.8 Hz, 2H).

10-Fluororutaecarpine (4bb). The same procedure described above for **4bd** was employed with 0.10 g (0.31 mmol) of hydrazone **3bc** to yield 65 mg (66%) of white needles after recrystallization from CH_3CN. mp 250 °C (sublimated). ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.08 (s, NH), 8.32 (dd, J = 8.0, 1.3 Hz, H_4), 7.73 (td, J = 8.3, 1.3 Hz, H_2), 7.67 (t, J = 8.3 Hz, 1H), 7.44 (td, J = 7.0, 1.4 Hz, 1H), 7.36 (td, J_{ortho} = 9.0 Hz, $^3J_{H\text{-}F}$ = 5.0 Hz, 1H), 7.28 (overlapped with $CDCl_3$, 1H), 7.10 (td, J_{ortho} = 9.0 Hz, $^3J_{H\text{-}F}$ = 2.5 Hz, 1H), 4.44 (t, J = 6.8 Hz, 2H), 3.15 (t, J = 6.8 Hz, 2H). ^{1}H NMR (250 MHz, DMSO-d_6) 12.08 (s, NH), 8.17 (dd, J = 8.0, 1.3 Hz, 1H), 7.82 (td, J = 8.3, 1.3 Hz, 1H), 7.52-7.43 (m, 3H), 7.10 (td, J_{ortho} = 9.0 Hz, $^3J_{H\text{-}F}$ = 2.5 Hz, 1H), 4.44 (t, J = 6.8 Hz, 2H), 3.15 (t, J = 6.8 Hz, 2H). *Anal.* Calcd for $C_{18}H_{12}FN_3O$: C, 70.81; H, 3.96; N, 13.76. Found: C, 71.07; H, 3.98; N, 13.78.

12-Chlororutaecarpine (4cd). The same procedure described above for **4bd** was employed with 0.72 g (2.13 mmol) of hydrazone **3ca** to yield 0.61 g (88%) of white needles. mp 217 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.9, 1.0 Hz, 1H), 7.84 (td, J = 8.3, 1.3 Hz, 1H), 7.78 (td, J = 7.3 Hz, 1H), 7.44 (td, J = 8.0, 0.9 Hz, 1H), 7.65 (dd, J = 8.0, 0.8 Hz, 1H), 7.51 (ddd, J = 8.9, 8.0, 1.0 Hz, 1H), 7.10 (dd, J = 9.0, 0.8 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 4.47 (t, J = 6.8 Hz, 2H), 3.19 (t, J = 6.8 Hz, 2H). *Anal.* Calcd for $C_{18}H_{12}ClN_3O$: C, 67.27; H, 3.76; N, 13.06. Found: C, 67.28; H, 3.82; N, 13.06.

9-Chlororutaecarpine (4ca) and 11-Chlororutaecarpine (4cc). The same procedure described above for **4bd** was employed with 0.27 g (0.80 mmol) of hydrazone **3cb** to yield 0.17 g (67%) of white needles, whose ^{1}H NMR spectrum showed presence of two isomers in a ratio of 4.5 : 5.5. The major component had a characteristic singlet at δ 7.73 for H12 which confirmed 11-chlororutaecarpine. Repeated recrystallization from EtOAc afforded 9-isomer as pure one: **9-Chlororutaecarpine**: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.08 (s, NH), 8.15 (d, J = 8.0 Hz, 1H), 7.81 (ddd, J = 8.3, 7.0, 1.0 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.70 (t, J = 8.2 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 160.77, 147.42, 145.20, 137.18, 134.71, 128.81, 126.82, 126.75, 126.46, 126.10, 124.91, 124.53, 121.02, 119.45, 117.53, 114.33, 40.98, 18.99. **11-Chlororutaecarpine**: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.08 (s, NH), 8.15 (d, J = 8.0 Hz, 1H), 7.81 (td, J = 8.3, 1.3 Hz, 1H), 7.73 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.25 (dd, J = 8.8, 2.0 Hz, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H).

10-Chlororutaecarpine (4cb). The same procedure described above for **4bd** was employed with 0.68 g (2.01 mmol) of hydrazone **3cd** to yield 0.46 g (71%) of white needles: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.07 (s, NH), 8.17 (dd, 1H, J = 7.9, 1.0 Hz), 7.83 (td, 1H, J = 7.5, 1.5 Hz), 7.77 (s, 1H), 7.64 (d, 1H, J = 8.0 Hz), 7.49 (ddd, 1H, J = 8.0, 7.6, 0.8 Hz), 7.11 (t, 1H, J = 7.8 Hz), 4.48-4.41 (m, 2H), 3.20-3.15 (m, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 160.74, 147.40, 144.97, 135.75, 134.65, 128.84, 127.12, 126.93, 126.75, 126.49, 124.59, 121.00 (two C's), 119.46, 117.17, 40.81, 19.14. *Anal.* Calcd for $C_{18}H_{12}ClN_3O$: C, 67.27; H, 3.76; N, 13.06. Found: C, 67.32; H, 3.78; N, 12.98.

12-Bromorutaecarpine (4dd). The same procedure described above for **4bd** was employed with 1.29 g (3.37 mmol) of hydrazone **3da** to yield 801 mg (65%) of white needles: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.08 (s, NH), 8.15 (d, J = 7.8 Hz, 1H), 7.81 (t, J = 7.0 Hz, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.62 (overlapped d, J = 8.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 160.76, 147.44, 145.18, 139.45, 134.71, 128.16, 126.82, 126.71, 126.43, 124.15, 123.00, 122.01, 121.00, 118.15, 117.71, 115.15, 40.98, 18.99. *Anal.* Calcd for $C_{18}H_{12}BrN_3O$: C, 59.04; H, 3.30; N, 11.47. Found: C, 59.08; H, 3.42; N, 12.06.

9-Bromoprutaecarpine (4da) and 11-Bromorutaecarpine (4dc). The same procedure described above for **4bd** was employed with 183 mg (0.48 mmol) of hydrazone **3db** to yield 152 mg (87%) of yellow needles. ^{1}H NMR showed two sets of spectrum, which confirmed the presence of two isomers of **9-bromorutaecarpine** (**4da**) and **11-bromorutaecarpine** (**4dc**). The attempts to separate these two isomers were not successful as yet. **9-Bromorutaecarpine**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.22 (s, NH), 8.14 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 7.5. 1.5

Hz, 1H), 7.48 (overlapped d, J = 7.8 Hz, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 4.44 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H). **11-Bromorutaecarpine**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.07 (s, NH), 8.14 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.36 (td, J = 8.3, 1.3 Hz, 1H), 7.25 (td, J = 8.8, 2.0 Hz, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.49 (t, J = 6.8 Hz, 2H).

10-Bromorutaecarpine (4db). The same procedure described above for **4bd** was employed with 194 mg (0.51 mmol) of hydrazone **3dc** to yield 145 mg (78%) of yellow needles: mp > 250 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.76 (s, NH), 8.15 (dd, J = 8.0, 1.3 Hz, H_4), 7.81 (ddd, J = 8.3, 7.8, 1.6 Hz, H_3), 7.67 (d, J = 7.7 Hz, H_1), 7.46 (td, J = 8.0, 1.2 Hz, H_2), 7.42 (s, H_9), 7.36 (d, J = 8.4 Hz, H_{12}), 7.09 (dd, J = 8.5, 1.4 Hz, H_{11}), 4.43 (t, J = 6.9 Hz, 2H), 3.15 (t, J = 6.9 Hz, 2H). *Anal.* Calcd for $C_{18}H_{12}BrN_3O$: C, 59.04; H, 3.30; N, 11.47. Found: C, 59.00; H, 3.32; N, 11.36.

12-Methanesulfonylrutaecarpine (4ed). The same procedure described for **4bd** was employed with 330 mg (0.87 mmol) of **3ea** to yield 202 mg (64%) of white needles: mp > 250 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.13 (s, N-H), 8.26 (d, J = 8.2 Hz, H1), 7.88 (t, J = 7.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.48 (overlapped t, J = 7.0 Hz, 2H), 7.10-7.05 (m, 2H), 4.44 (t, J = 6.8 Hz, 2H), 3.21 (t, J = 6.8 Hz, 2H), 3.21 (s, 3H). *Anal.* Calcd for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.42; H, 4.17; N, 11.46.

10-Methanesulfonylrutaecarpine (4eb). The same procedure described above for **3ba** with 400 mg (1.87 mmol) of **1** and 403 mg (2.61 mmol) of 2-methanesulfonylphenylhydrazineHCl to afford 680 mg (95%) of pale yellow needles which was not characterized but instead subjected to the same procedure described above for **4bd** to yield 368 mg (58%) of white needles. mp > 300 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.48 (s, NH), 8.28 (d, J = 8.3 Hz, H15), 8.14 (dd, 1H, J = 8.9, 1.1 Hz), 7.77 (td, 1H, J = 8.3, 1.3 Hz), 7.83 (td, 1H, J = 7.3 Hz), 7.75 (td, 1H, J = 8.0, 0.9 Hz), 7.68-7.44 (m, 2H), 7.48 (td, 1H, J = 8.0, 0.8 Hz), 4.45 (t, 2H, J = 6.8 Hz), 3.21 (t, 2H, J = 8.8 Hz), 3.19 (s, 3H). *Anal.* Calcd for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.50; H, 4.12; N, 11.56.

12-Methylrutaecarpine (4fd). The same procedure described above for **4bd** with 120 m g (0.38 mmol) of **3fa** to yield 85 mg (75%) of white needles. mp > 300 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.71 (s, NH), 8.15 (dd, 1H, J = 8.0, 1.2 Hz, H4), 7.81 (td, 1H, J = 6.8, 1.2 Hz), 7.74 (td, 1H, J = 7.0, 0.8 Hz), 7.47 (overlapped td, 2H, J = 7.0, 1.2 Hz), 7.05 (d, 1H, J = 6.8 Hz), 6.99 (t, 1H, J = 7.3 Hz), 4.44 (t, 2H, J = 6.8 Hz), 3.15 (t, 2H, J = 6.8 Hz), 2.56 (s, 3H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 160.88, 147.64, 145.55, 138.49, 134.67, 127.43, 126.81, 126.74, 126.20, 126.58, 125.02, 122.43, 120.90, 120.27, 118.94, 117.65, 40.99, 19.23, 17.55. *Anal.* Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.69; H, 5.10; N, 14.03.

9-Methylrutaecarpine (4fa) and 11-Methylrutaecarpine (4fc). The same procedure described above for **4bd** with 120 m g (0.38 mmol) of **3fb** to yield 89 mg (78%) of yellow needles. ^{1}H NMR showed two sets of spectum, which confirmed the presence of two isomers of **9-methylrutaecarpine** (**4fa**) and **11- methylrutaecarpine** (**4fc**) in a ratio of 1 : 2. The attempts to separate these two isomers were not successful as yet. **9-Methylrutaecarpine**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.83 (s, NH), 8.14 (dd, 1H, J = 8.0, 1.2 Hz, H4), 7.80 (td, 1H, J = 8.0 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.4 Hz), 7.11 (t, 1H, J = 8.3 Hz), 6.78 (d, 1H, J = 8.3 Hz), 4.43 (t, 2H, J = 6.9 Hz), 3.15 (t, 2H, J = 6.9 Hz), 2.61 (s, 3H). **11-Methylrutaecarpine**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.74 (s, NH), 8.14 (dd, 1H, J = 8.0, 1.2 Hz, H4), 7.80 (td, 1H, J = 8.0 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.4 Hz), 7.25 (s, 1H), 6.92 (d, 1H, J = 8.3 Hz), 4.43 (t, 2H, J = 6.9 Hz), 3.39 (t, 2H, J = 6.9 Hz), 2.41 (s, 3H).

10-Methylrutaecarpine (4fb). The same procedure described above for **4bd** with 120 m g (0.38 mmol) of **3fc** to yield 85 mg (75%) of white needles: mp > 300 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.76 (s, NH), 8.15 (dd, 1H, J = 8.0, 1.2 Hz, H4), 7.83-7.77 (m, 2H), 7.66 (d, H, J = 7.7 Hz), 7.46 (td, 1H, J = 8.0, 1.2 Hz), 7.41 (s, H9), 7.35 (d, 1H, J = 8.4 Hz), 7.09 (dd, 1H, J = 8.3, 1.4 Hz), 4.43 (t, 2H, J = 6.9 Hz), 3.15 (t, 2H, J = 6.9 Hz), 2.48 (s, 3H). ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 160.85, 147.63, 145.60, 137.34, 134.67, 128.64, 127.31, 126.84 (2 C's), 126.64, 126.16, 125.30, 120.88, 119.46, 117.59, 41.05, 21.38, 19.16. *Anal.* Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.71; H, 5.01; N, 13.93.

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