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Synthesis of 8-Substituted 7-Azarutaecarpines[1]

Árpád Kiss,[a] József Kökösi,[a] Réka Rotter[a] and István Hermecz[b,*]

[a]*Institute for Pharmaceutical Chemistry, Semmelweis University of Medicine, H-1092 Budapest, Högyes E u. 9, Hungary*
[b]*CHINOIN Pharmaceutical and Chemical Works Ltd, H-1045 Budapest, Tó u. 1-5, Hungary*

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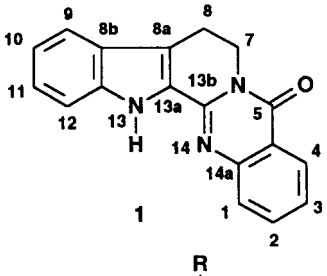
Abstract—The synthesis of 8-substituted 7-azarutaecarpines **2** is described. These compounds were prepared by Fischer indolization of 3-amino-2-(1-phenylhydrazonoethyl)-4(3*H*)-quinazolinone **5**, followed by cyclocondensation with a series of aliphatic, araliphatic or aromatic aldehydes and formic acid or a Vilsmeier–Haack reagent. The stereochemistry of compounds **2** was investigated by ^{1}H NMR spectroscopy. It was found that the 8-substituents assume a quasi-axial position on the flattened boat conformation of ring C of **2**, with the exception of *ortho* substituted phenyl groups, which occupy quasi-equatorial positions. Semi-empirical MO calculations support these conformational preferences.

Introduction

Rutaecarpine **1** (7,8-dihydro-5*H*,11*H*-indolo[2,3;3′,4′]-pyrido[2,1-*b*]quinazolin-5-one) belongs among the quinazolinocarboline-type alkaloids isolated from the genera *Evodia*, *Hortia*, *Zanthoxylum*, *Euxylophora* and *Phellodendron*, all members of the Rutaceae.[2,3] Rutaecarpine **1** and its substituted derivatives are constituents of traditional Chinese folk medicines. The Chinese crude drug, the bark of *Phellodendron amurense* Rupr., has been used as a stomachic for intestinal function control and as an antibacterial and anti-inflammatory agent.[4] The isolation and identification of 7-hydroxy- and 7,8-dihydroxyrutaecarpines from the callous tissue of stems of this species[5] were recently reported. Rutaecarpine **1**, evodiamine and dehydroevodiamine are the bioactive compounds of the Chinese herbal drug, Wu-Chu-Yu,[6] the dried unripened fruit of *Evodia rutaecarpa* (Juss.) Benth. Wu-Chu-Yu has traditionally been used for the treatment of abdominal pain, gastrointestinal disorders, headache, dysentery, postpartum haemorrhage and amenorrhoea.[7]

Pharmacological effects of the bioactive components of *Evodia rutaecarpa* have been reported in the literature.[8–20] Rutaecarpine **1** and its natural derivatives (evodiamine and dehydroevodiamine) command interest as hypertensive, diuretic, uterotonic, positive inotropic and platelet aggregation inhibitory agents. Cerebral anti-anoxic, vasorelaxant, anti-cholinesterase and anti-amnesic activities of these alkaloids were recently discovered. The hypotensive, antiarrhythmic, anti-anoxic and vasorelaxant effects have been investigated more intensively, and synthetic and pharmacological development in this field may lead to therapeutic applications.

We earlier developed[21,22] facile total syntheses of rutaecarpine alkaloid **1**, starting from 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one alkaloid,[23] via Fischer indolization of 6-phenylhydrazono-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one.[21] We later extended this new approach to the synthesis of derivatives of rutaecarpine **1** substituted in rings A, C and E,[24] their 1,2,3,4-tetrahydro derivatives,[25] C-ring homologues,[26] opened analogues[27] and E-ring debenzo derivatives[28] and 3-aza analogues.[29]



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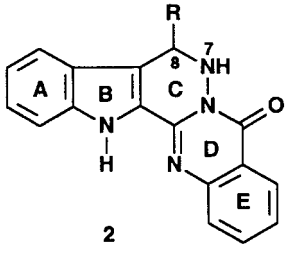

2

In a continuation of such studies, we now describe the preparation of 8-substituted 7-aza derivatives **2** of rutaecarpine **1** by Fischer indolization of 3-amino-2-(1-phenylhydrazonoethyl)-4(3*H*)-quinazolinone **5**, followed by

Keywords: nitrogen heterocycles; Fischer reactions; cyclocondensation; conformation.

* Corresponding author. Tel.: +361-369-0151; fax: +361-370-5597; e-mail: istvan.hermecz@sanofi.com

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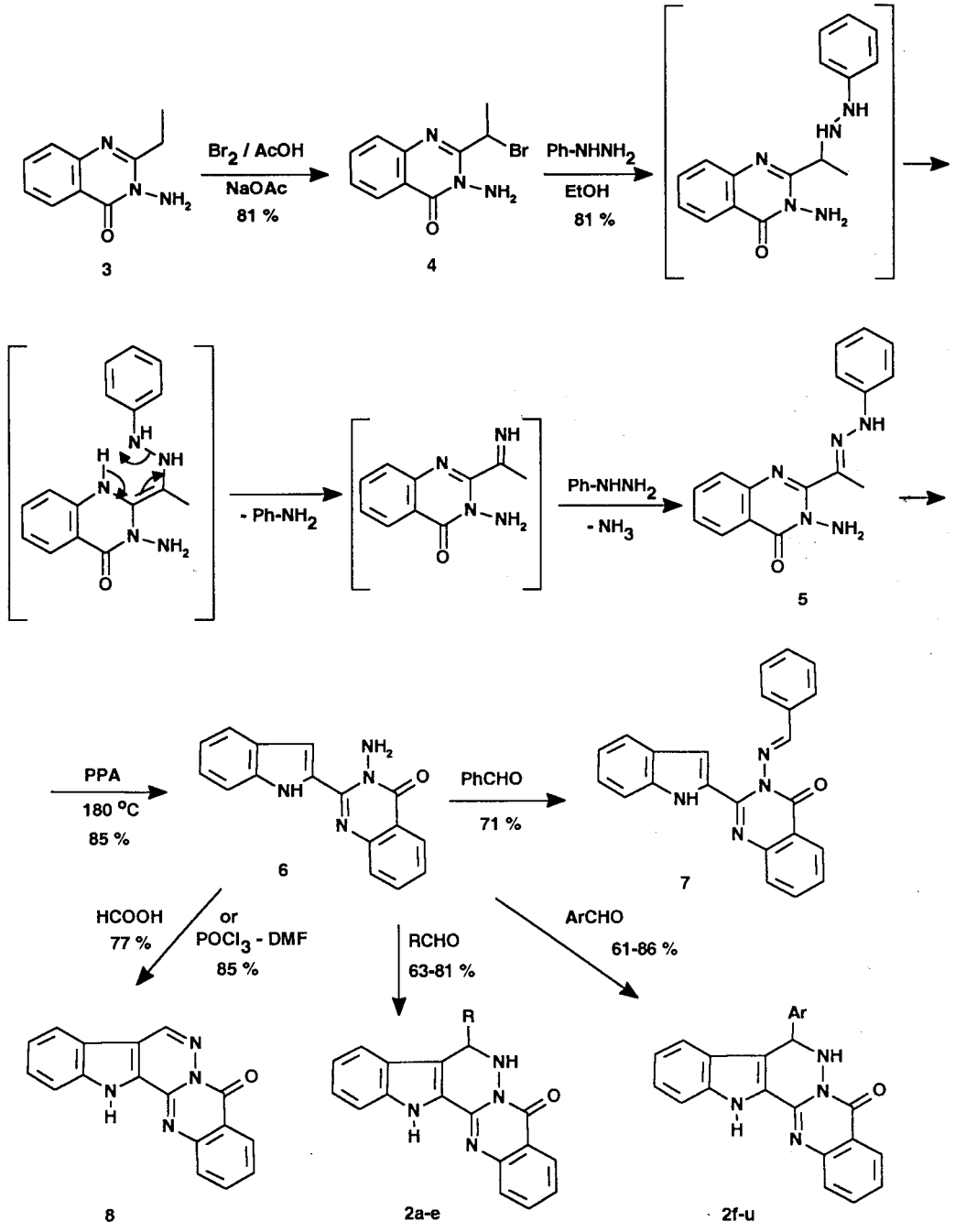


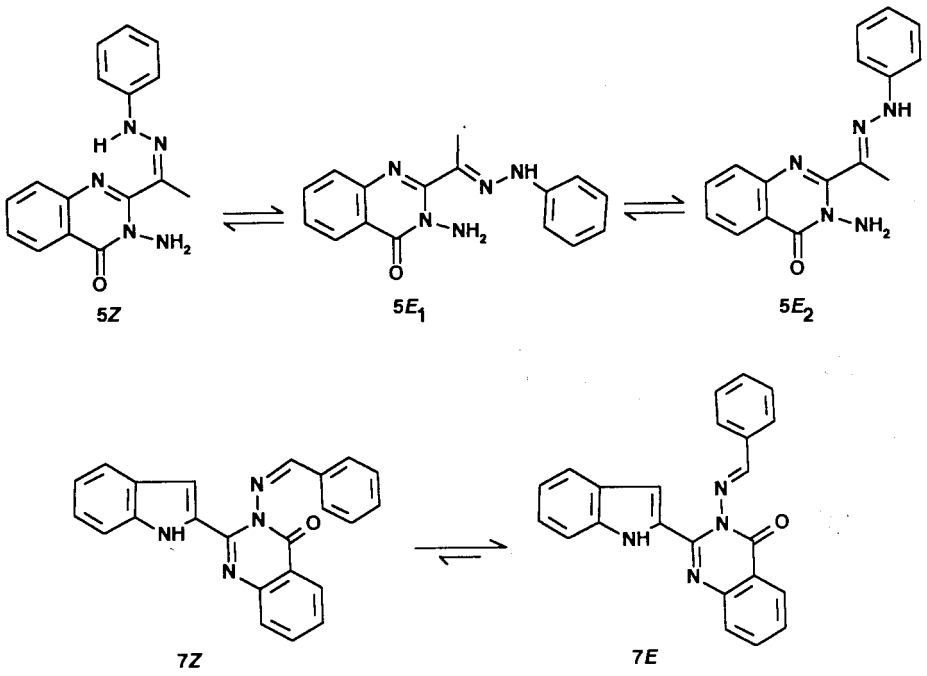
Scheme 1.

cyclocondensation with aldehydes. The compounds **2** are the first representatives of the pentacyclic ring system indolo[2,3;4′,5′]pyridazino[2,1-*b*]quinazoline. Only the unsubstituted derivative **2a** has been described earlier.[30]

Results and Discussion

In order to develop new drugs from natural products via structural modification of their ring systems, we have examined an original synthetic approach for preparation of the indolo-pyridazino-carboline ring system.

The synthesis of 7-aza analogues **2** of rutaecarpine **1** is based on the fact that 2-alkylquinazolones contain an active methylene group in the α-position of the side-chain. The starting 2-ethyl-3-amino-4(3*H*)-quinazolin-4-one **3**, prepared from commercially available compounds by the reaction of 2-alkylbenzoxane with hydrazine hydrate via a literature method,[31] was brominated in acetic acid solution with bromine in the presence of sodium acetate at 40°C to give bromo derivative **4** in good yield. The reaction of bromo derivative **4** with phenylhydrazine involves nucleophilic substitution, with a subsequent oxidation process analogous to the formation of osazones to afford 2-(1-phenylhydrazonoethyl)-3-amino-4(3*H*)-quinazolinone **5** (see Scheme 1). For a good yield (81%), 2 mol of hydrazine should be applied. Phenylhydrazone derivative



Scheme 2.

5 exhibits a solvent-dependent *E–Z* geometric isomerism (Scheme 2). The interconversion of the *E* and *Z* isomers requires low activation energy, as equilibrium mixtures were obtained in either $CDCl_3$ or DMSO-d_6 immediately after dissolution of phenylhydrazone **5**. The ratio of the **5***E* and **5***Z* isomers was determined from the intensity of the NH-group signal of the hydrazono moiety in the NMR spectra of the compound. In $CDCl_3$ solution, the signals of the NH protons appear as a broadened peak in region 13.4–14.6 ppm, indicating a H-bond of considerable strength. The **5***E*$_1$:*Z* ratio was found to be 62:38. The existence of the sterically more hindered **5***Z* isomer in chloroform can be explained by the gain in energy due to the formation of an internal H-bond between N-1 of the quinazolone ring and the NH group in the side-chain of the phenylhydrazone. The predominance of the **5***E* isomer in the equilibrium is due to the more favourable steric arrangement and the formation of another intramolecular H-bond between the 3-amino group and the imino nitrogen of the phenyhydrazono group. In DMSO-d_6, a solvent forming stronger H-bonds with amino groups, the predominance of the sterically more favourable *E* form is increased. On the basis of the NH

Table 1. Physical and analytical data on 8-substituted 7-azarutaecarpines (**2**)

Compound no.	R	Mp (°C)	Yield (%)	Formula (mol. weight)	Analysis (calc. /found %)		
					C	H	N
2a	H-	142–143	64	$C_{17}H_{12}N_4O$ (288.309)	70.82 (70.87)	4.20 (4.21)	19.43 (19.37)
2b	Et-	289–290	63	$C_{19}H_{16}N_4O$ (316.364)	72.14 (72.19)	5.10 (5.16)	17.71 (17.75)
2c	$PhCH_2$-	297–299	74	$C_{24}H_{18}N_4O$ (378.435)	76.17 (76.11)	4.79 (4.73)	14.80 (14.82)
2d	PhCH=CH-	275–278	81	$C_{25}H_{18}N_4O$ (390.446)	76.91 (76.99)	4.65 (4.57)	14.35 (14.30)
2e	4-MeNPhCH=CH-	348–350	80	$C_{27}H_{23}N_5O$ (433.515)	74.81 (74.85)	5.35 (5.39)	16.15 (16.10)
2f	4-AcNHPH-	252–254	76	$C_{25}H_{19}N_5O_2$ (421.460)	71.25 (71.19)	4.54 (4.51)	16.62 (16.55)
2g	4-Me_2NPh-	265–267	72	$C_{25}H_{21}N_5O$ (407.477)	73.69 (73.60)	5.19 (5.10)	17.19 (17.12)
2h	3,4-di-MeOPh-	218–220	68	$C_{25}H_{20}N_4O_3$ (424.460)	70.74 (70.79)	4.75 (4.69)	13.20 (13.27)
2i	3,4-di-HOPh-	250–254	78	$C_{23}H_{16}N_4O_3$ (396.396)	69.69 (69.61)	4.07 (4.08)	14.13 (14.19)
2j	4-MeOPh-	252–254	85	$C_{24}H_{18}N_4O_2$ (394.543)	73.08 (73.17)	4.60 (4.63)	14.20 (14.14)
2k	3-HOPh-	260–262	73	$C_{23}H_{16}N_4O_2$ (380.507)	72.62 (72.57)	4.24 (4.29)	14.73 (14.68)
2l	4-MePh-	257–260	68	$C_{24}H_{18}N_4O$ (378.535)	76.17 (76.09)	4.79 (4.73)	14.80 (14.85)
2m	Ph-	304–306	86	$C_{23}H_{16}N_4O$ (364.508)	75.81 (75.79	4.43 (4.39)	15.37 (15.30)
2n	3-ClPh-	255–258	76	$C_{23}H_{15}ClN_4O$ (398.853)	69.26 (69.20)	3.79 (3.70)	14.05 (14.09)
2o	4-BrPh-	241–245	64	$C_{23}H_{15}BrN_4O$ (443.304)	62.32 (62.37)	3.41 (3.44)	12.64 (12.63)
2p	4-MeOOCPh-	333–335	68	$C_{25}H_{18}N_4O_3$ (422.444)	71.08 (71.15)	4.29 (4.29)	13.26 (13.18)
2q	2-furyl-	237–241	61	$C_{21}H_{14}N_4O_2$ (354.369)	71.18 (71.12)	3.98 (3.95)	15.81 (15.76)
2r	2-thienyl-	231–234	67	$C_{21}H_{14}N_4OS$ (369.436)	68.09 (68.16)	3.81 (3.88)	15.12 (15.16)
2s	3-indolyl-	322–323	63	$C_{25}H_{17}N_5O$ (403.445)	74.43 (74.47)	4.25 (4.20)	17.36 (17.34)
2t	2-ClPh-	157–159	72	$C_{23}H_{15}ClN_4O$ (398.853)	69.26 (69.19)	3.79 (3.73)	14.05 (14.01)
2u	2-NO_2Ph-	308–311	68	$C_{23}H_{15}N_5O_3$ (409.405)	67.48 (67.40)	3.69 (3.62)	17.11 (17.07)

Table 2. UV data on 8-substituted 7-azarutaecarpines (**2**) (i=inflexion)

Compound no.	λ_{max} (log ϵ)
2a	368 (4.43), 348 (4.51), 326 (4.44), 312 (4.05), 274 (4.16), 220 (4.54)
2b	366 (4.39), 348 (4.47), 340 (4.40), 278 (4.22), 242 (4.42), 214 (4.49)
2c	362 (4.39), 346 (4.39),332 (4.33), 255 (4.04), 246I, 216 (4.42)
2d	330 (4.43), 240 (4.03), 212 (4.46)
2e	370 (4.42), 350 (4.38), 330 (4.28), 282 (4.11), 272 (4.05), 236I, 214 (4.45)
2f	364 (4.43), 346 (4.34), 332 (4.27), 248 (4.31), 212 (4.37)
2g	364 (4.28), 346 (4.36), 332 (4.29), 258 (4.31), 216 (4.39)
2h	364 (4.26), 346 (4.34), 332 (4.27), 286 (3.95), 250i, 214 (4.37)
2i	362 (4.29), 348 (4.37), 336 (4.30), 284 (4.17), 210 (4.39)
2j	362 (4.29), 346 (4.38), 330 (4.31), 292 (4.22), 248i, 222 (4.40)
2k	364 (4.31), 346 (4.39), 332 (4.32), 250 (4.15), 220 (4.42)
2l	364 (4.31), 346 (4.39), 332 (4.33), 250 (4.12), 220 (4.42)
2m	364 (4.33), 346 (4.35), 332 (4.34), 250i, 216 (4.44)
2n	362 (4.29), 346 (4.37), 332 (4.30), 275 (4.09), 214 (4.39)
2o	364 (4.26), 346 (4.35), 332 (4.26), 250i, 220 (4.35)
2p	364 (4.26), 346 (4.34), 334 (4.27), 288 (3.99) 250i, 234 (4.37)
2q	362 (4.34), 346 (4.35), 332 (4.34), 250 (4.14), 220 (4.45)
2r	362 (4.33), 346 (4.35), 332 (4.33), 220 (4.43)
2s	336 (4.34), 306 (4.34), 280 (3.98), 224 (4.41)
2t	362 (4.29), 346 (4.37), 332 (4.30), 216 (4.39)
2u	364 (4.27), 346 (4.35), 332 (4.28), 278 (4.02), 250i, 218 (4.36)

group signals, the *E*:*Z* ratio is 94:6 in DMSO-d_6 for compound **5**. The **5***E* isomer exists in two different conformers (**5***E*$_1$ and **5***E*$_2$) in a ratio of 26:74.

Fischer indolization of phenylhydrazone compound **5** was carried out in polyphosphoric acid at 180–185°C to give 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6**. This compound was earlier isolated by Bergman[30,32] during investigation of the rearrangement reaction of indigo with hydrazine hydrate.

The hydrazide **6** readily condensed with benzaldehyde in ethanol at room temperature to yield the corresponding benzylidene derivative **7**. Compound **7** was obtained as a mixture of *E*–*Z* geometric isomers, as reflected by its ^{1}H NMR spectrum in $CDCl_3$. Because of geometrical isomerization the signals of the CH═N methine protons appeared as a pair of singlets at 7.98 and 8.21 ppm (an *E*–*Z* ratio of 9:1), owing to the different steric arrangement in the stereoisomers. The steric arrangement might be attributed to the hindered rotation of the azomethine linkage.

The reactions of 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6** with aliphatic aldehydes in ethanol at reflux temperature in the presence of a catalytic amount of hydrochloric acid led to ring closed products **2a**,**b**. The reactions of **6** with a series of araliphatic and (hetero)aromatic aldehydes at higher temperature (120–140°C in dimethylformamide) led to cyclization of the azomethine-type intermediate **7** and gave directly the pentacyclic ring-closed products, 8-substituted indolo[2,3;4′,5′]pyridazino[2,1-*b*]-quinazolin-5-ones **2c**–**u**. Use of the minimum amount of DMF as solvent in the condensation reaction gave products with higher purity and in better yield (Table 1).

The UV spectra of **2** showed the presence of a highly conjugated system with absorption bands characteristic of indolopyridoquinazoline-type alkaloids[2,25] (Table 2). The high similarity of the chromophore of aza analogues **2** to the natural alkaloids[2] indicated that the nitrogen substituents at position 7 and the different substituents on C-8 have only a slight influence on the conjugated system of the pentacyclic compounds.

Because of the highly conjugated nature of **2**, the indole and quinazolone moieties have a coplanar orientation. Ring C of the pentacyclic system has only multiplanar conformational flexibility. In order to determine the conformational preferences of **2**, we investigated the stereochemistry of the compounds by ^{1}H NMR spectroscopy in solution. ^{1}H NMR chemical shifts and coupling constants are listed in Table 3.

In the aromatic region of the ^{1}H NMR spectra, two pairs of four mutually coupled protons were characteristic of *ortho*-disubstituted benzoid rings. The signals of the 7-NH and 8-CH protons appear as doublets in the spectra of **2**; the vicinal coupling constants $^3J_{8H,7\text{-}NH}$ are reported in Table 3. Through use of the measured coupling constants, we could calculate the dihedral angles H_7–N_7–C_8–H_8 by applying the Karplus equation.[33–35] The calculated values of the dihedral angles are Φ=53–55° for the phenyl compound, all *meta* and *para*-substituted derivatives **2f**–**p** and the heteroaromatic compounds **2q**–**s**. For the *ortho*-substituted compounds **2t**,**u**, the dihedral angle is Φ=46–47°. For interpretation of the significant differences between the *ortho* **2t**,**u** and the *para* or *meta* analogues **2f**–**p**, molecular modelling via semi-empirical MO calculations (the PM3 method in the HYPERCHEM program package) was used to predict the configurational and conformational preferences of **2**. The geometrical optimization of the 8-phenyl compound **2m** and 8-(*ortho*-nitrophenyl) compound **2u** resulted in different global energy minimum conformations for ring C (Fig. 1).

The 8-phenyl substituent in the derivative **2m** occupies a quasi-axial position on the flattened (at fragment C14*a*-C13*a*-C8*a*) boat conformation of the heterocyclic ring. The calculated dihedral angle H_7–N_7–C_8–H_8 in the geometrically optimized structure was 52.8° (conformer A). The 8-aryl substituents with similar coupling constants among the *meta* and *para*-substituted derivatives **2f**–**p** should assume the quasi-axial positions.

For the *ortho*-substituted derivatives **2t**,**u**, the values of the 8-H proton chemical shifts and coupling constants $^3J_{8H,7\text{-}NH}$ are indicative of the steric arrangement of the 8-aryl

Table 3. ^{1}H NMR data on 8-substituted 7-azarutaecarpines (**2**) in $CDCl_3$

Compound no.	H-1[a]	H-2[b]	H-3[c]	H-4[d]	NH-7[e]	H-8[f] ($^3J_{8H,7H}$)	H-9[g]	H-10[h]	H-11[i]	H-12[j]	NH-13[k]	Others
2a	7.62	7.73	7.38	8.21	9.58	2.96[l] (3.13)	7.65	7.18	7.36	7.46	7.32	
2b	7.62	7.73	7.38	8.25	9.28	5.51[m] (2.74)	7.65	7.18	7.36	7.46	7.32	0.95 (3H, t, J~7.4 Hz, CH_3), 1.87 (2H, dq, $J_{CH2,8\text{-}H}$~6.5 Hz, CH_2)
2c	7.59	7.70	7.39	8.88	9.38	5.53[n] (2.69)	7.65	7.18	7.36	7.46	7.32	2.83 (2H, d, $J_{CH2,8\text{-}H}$~6.8 Hz, CH_2Ph), 7.26–7.43 (5H, m, Ph)
2d	7.60	7.72	7.38	8.96	9.46	5.64[o] (2.64)	7.63	7.16	7.34	7.45	7.31	5.67 (1H, dd, $J_{=CH-C(8)H}$~6.3 Hz, =C*H*-C8), 6.78 (1H, d, $J_{\text{-}CH=CH\text{Ph}}$~16 Hz, =C*H*-Ph), 7.22–7.39 (5H, m, Ph)
2e	7.57	7.69	7.34	8.18	9.26	5.61[p] (2.67)	7.62	7.15	7.32	7.41	7.28	2.91 (6H, s, NMe_2), 5.49 (1H, dd, $J_{=CH\text{-}C(8)H}$~6.5 Hz, =C*H*-C8), 6.64 (1H, d, $J_{\text{-}CH=CH\text{Ph}}$~16 Hz, =C*H*-Ph), 6.83 (2H, d, J~7.8 Hz, 3‴,5′-H), 7.17 (2H,d, 2′,6′-H)
2f	7.61	7.72	7.36	8.25	9.29	5.74 (2.61)	7.67	7.16	7.35	7.46	7.30	2.08 (3H, s, CH_3), 6.82 (2H, d, J~8.1 Hz, 3′,5′-H), 7.23 (2H, d, 2′,6′-H), 9.50 (1H, s, NHCO)
2g	7.58	7.70	7.35	8.20	9.01	5.68 (2.45)	7.60	7.19	7.33	7.42	8.28	2.88 (6H, s, NMe_2), 6.76 (2H, d, J~7.7 Hz, 3′,5′-H), 7.14 (2H,d, 2′,6′-H)
2h	7.64	7.75	7.39	8.28	9.29	5.79 (2.52)	7.67	7.19	7.37	7.47	7.34	3.75 (3H, s, 3-MeO), 3.91 (3H, s, 4-MeO), 6.80 (1H, d, J~8.0 Hz, 5′-H), 7.18 (1H, d, 6′-H), 7.27 (1H, s, 2′-H),
2i	7.60	7.71	7.37	8.24	9.16	5.74 (2.54)	7.63	7.16	7.34	7.45	7.30	4.77 (2 **H**, s, OH), 6.91 (1H, d, J~8.0 Hz, 5′-H), 7.16 (1H, d, 6′-H), 7.21 (1H, s, 2′-H)
2j	7.59	7.70	7.36	8.23	9.26	5.75 (2.44)	7.63	7.16	7.33	7.43	7.32	3.83 (3H, s, 4-OMe), 6.82 (2H, d, J~7.7 Hz, 3′,5′-H), 7.16 (2H,d, 2′,6′-H)
2k	7.60	7.71	7.34	8.27	9.30	5.72 (2.39)	7.61	7.21	7.38	7.43	7.48	5.68 (1 **H**, s, OH), 7.24–7.33 (4H, m, Ph)
2l	7.58	7.72	7.39	8.28	9.40	5.73 (2.41)	7.65	7.18	7.36	7.46	7.37	2.48 (3H, s, Me), 6.98 (2H, d, J~8.0 Hz, 3′,5′-H), 7.52 (2H, d, 2′,6′-H)
2m	7.58	7.71	7.37	8.22	9.42	5.73 (2.40)	7.64	7.19	7.34	7.45	7.43	7.29–7.45 (5H, m, Ph)
2n	7.60	7.71	7.34	8.27	9.48	5.72 (2.39)	7.61	7.21	7.38	7.43	7.38	7.28–7.37 (4H, m, Ph)
2o	7.60	7.71	7.34	8.27	9.52	5.72 (2.44)	7.61	7.21	7.38	7.43	7.38	7.35 (2H, d, J~8.2 Hz, 3′,5′-H), 7.62 (2H, d, 2′,6′-H)
2p	7.62	7.74	7.39	8.38	9.31	5.96 (2.39)	7.68	7.20	7.36	7.46	8.34	3.99 (3H, s, MeO), 6.87 (2H, d, J~7.9 Hz, 3′,5′-H), 7.76 (2H, d, 2′,6′-H)
2q	7.58	7.71	7.37	8.22	9.28	5.73 (2.53)	7.64	7.19	7.34	7.45	7.43	6.23 (1H, dd, 4′-H), 6.48 (1H, d, $J_{3',4'}$~4.0 Hz, 3′-H), 6.84 (1H, d, $J_{4',5'}$~3.5 Hz, 5′-H)
2r	7.59	7.72	7.39	8.28	9.25	5.73 (2.51)	7.65	7.18	7.36	7.46	7.39	6.63 (1H, dd, 4′-H), 6.76 (1H, d, $J_{3',4'}$~3.5 Hz, 3′-H), 7.04 (1H, d, $J_{4',5'}$~3.5 Hz, 5′-H)
2s	7.61	7.73	7.40	8.48	9.40	5.73 (2.84)	7.65	7.18	7.36	7.46	7.47	6.94 (1H, s, 2′-H), 7.03 (1H, d, $J_{4',5'}$~8.3 Hz, 4′-H), 7.20(1H, dd, $J_{5',6'}$ 8.0 Hz, 6′-H), 7.28 (1H, d, $J_{6',7'}$~8.0 Hz, 7′-H), 7.65 (1H, dd, 5′-H)
2t	7.61	7.72	7.34	8.28	10.34	6.17 (3.59)	7.61	7.21	7.38	7.43	8.48	7.01 (1H, d, $J_{5',6'}$~7.4 Hz, 6′-H), 7.38 (1H, dd, $J_{4',5'}$~7.4 Hz, 4′-H), 7.42 (1H, dd, 5′-H), 7.64 (1H, d, $J_{3',4'}$~7.4 Hz, 3′-H)
2u	7.63	7.78	7.41	8.38	10.57	6.41 (3.68)	7.70	7.23	7.38	7.51	8.63	7.51 (1H, d, $J_{5',6'}$~8.3 Hz, 6′-H), 7.68 (1H, dd, $J_{4',5'}$~8.2 Hz, 4′-H), 7.79 (1H, dd, 5′-H), 8.11 (1H, d, $J_{3',4'}$~8.2 Hz, 3′-H)

[a] 1H, dd, $J_{1,2}$~8 Hz, $^4J_{1,3}$~1.5 Hz.
[b] 1H, ddd, $J_{2,3}$~7.6 Hz; $^4J_{2,4}$~1.5 Hz.
[c] 1H, ddd, $J_{3,4}$~7.6 Hz.
[d] 1H, dd.
[e] 1H, d.
[f] 1H, d.
[g] 1H, dd, $J_{9,10}$~7.5 Hz, $^3J_{9,11}$~1 Hz.
[h] 1H, ddd, $J_{10,11}$~7.5 Hz, $^3J_{10,12}$~1 Hz.
[i] 1H, ddd, $J_{11,12}$~8.5 Hz.
[j] 1H, dd.
[k] 1H, s.
[l] 2H, d.
[m] 1H, dt, $J_{CH2,8\text{-}H}$~6.5 Hz.
[n] 1H, dt, $J_{CH2,8\text{-}H}$~6.8 Hz.
[o] 1H, dd, $J_{CH,8\text{-}H}$~6.3 Hz.
[p] 1H, dd, $J_{CH,8\text{-}H}$~6.5 Hz.

substituents. In the spectra of the *ortho*-substituted derivatives **2t**,**u** upfield shifts of the 8-H proton signal (0.4–0.7 ppm) are observed. In the spectra of the *ortho*-chloro derivative **2t**, this signal is shifted upfield by ca. 0.4 ppm in relation to the *meta* and *para* derivatives **2f**–**p**, whereas in the spectra of the *ortho*-nitro derivative **2u**, the upfield shift observed is even larger and reaches ca. 0.7 ppm. Both the chemical shift and the coupling constants indicate the quasi-axial orientation of the proton in position 8 in compounds **2t**,**u**. As Fig. 1 clearly shows for the *ortho*-nitrophenyl derivative **2u**, the results of MO calculations support the conformational change of the molecule, in agreement with the effect observed in the NMR spectra. The results of both approaches permit the conclusion that the amine bond in **2t**,**u** is significantly twisted as a result of steric hindrance of the bulky *ortho*-substituted phenyl group. In conformer B, the NH proton has a quasi-equatorial position and is shifted upfield by ca. 1.5 ppm, which may be explained in the terms of the effect of the neighbouring carbonyl group. The dihedral angles calculated from the experimental coupling constants of **2u** by using a basic Karplus equation are in good agreement with the calculated values estimated from the geometrically optimized structure of **2u**. In conformer B, the ring C has a nearly planar conformation, as a result of steric and electronic interactions between the aromatic π-orbitals of the indole ring and the bulky *ortho*-substituted phenyl

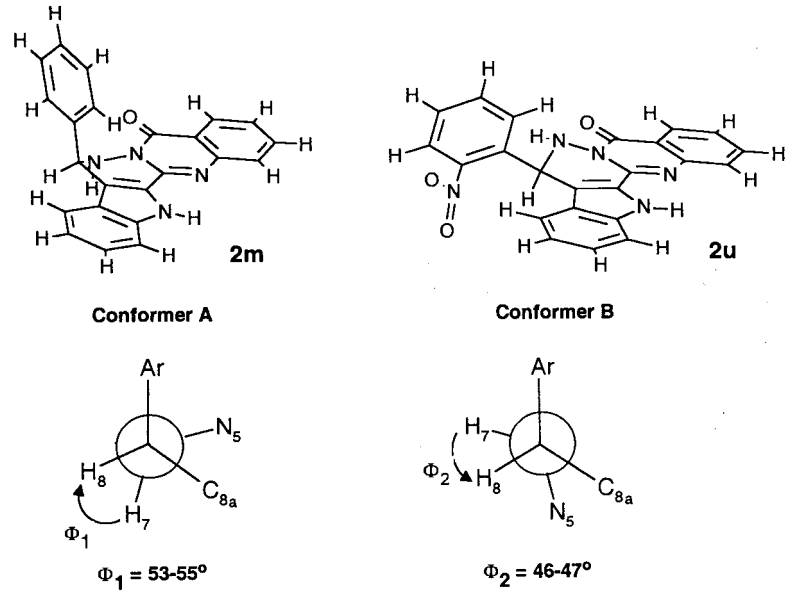


Figure 1. ISIS drawing of computer-generated structures of **2m** and **2u**, optimized by the PM3 method in the HYPERCHEM package, in a view which reveals all atoms, and Newman projections of substituents around the N_7–C_8 bond.

ring bearing a substituent with lone pairs of electrons (NO_2, Cl).

A detailed ^{1}H NMR study and additional molecular modelling calculations led us to conclude that the 8-substituted 7-azarutaecarpines **2** do not have a homogeneous conformation, and two different conformers must be taken into account, containing the 8-substituent in the quasi-axial or quasi-equatorial orientation.

Finally, the condensation of 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6** with formic acid at 120°C for 6 h or with a Vilsmeier–Haack reagent at 55°C for 2 h readily led to the formation of 5*H*,13*H*-indolo[2,3;4′,5′]pyridazino[2,1-*b*]-quinazolin-5-one **8**, which is the aza analogue of the antimutagenic 7,8-dehydrorutaecarpine.[36]

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. The yields were not maximized. The UV spectra were recorded in ethanol with a Unicam SP-800. The IR spectra were taken in KBr disks on a Pye Unicam Sp-1100 IR spectrometer. The ^{1}H NMR spectra were registered in $CDCl_3$ or DMSO-d_6 on a Bruker DRX-400 spectrometer at 400.13 MHz (TMS was used as internal standard). Elementary analyses (C,H,N) were performed with a Perkin–Elmer 2400 CHN Analyzer. The dihedral angle (Φ) was estimated from the coupling constants $^3J_{7H,8H}$ using the basic Karplus equation $^3J_{7H,8H}$= 4.5×cos2Y−0.5×cosY+4.22. Semi-empirical quantum chemical calculations (HYPERCHEM program, PM3 method) were performed on a Silicon Graphics Indigo Solid Impact workstation.

3-Amino-2-(1′-bromoethyl)-4(3*H*)-quinazolinone (4). To a mixture of 3-amino-2-ethyl-4(3*H*)-quinazolinone[31] **3** (1.89 g, 10 mmol), and sodium acetate (0.82 g, 10 mmol) in glacial acetic acid (20 ml) was added bromine (1.60 g, 10 mmol) in glacial acetic acid (10 ml) dropwise at 40–50°C. The reaction mixture was stirred for 3 h, and it was then left to stand in a refrigerator overnight. The crystals were filtered off, washed with water and recrystallized from 2-propanol, to give 2.1 g (81%) of compound **4** as a white solid, mp 170–171°C. $UV_{(EtOH)}$ λ_{max}(log ϵ): 407 (3.63), 320 (3.75), 305 (3.87), 283 (3.84), 227 (4.18); $IR_{(KBr)}$ ν_{max}: 3360, 3300, 1686, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.07 (3H, d, *J*=7.1 Hz,CH*Me*), 4.92 (1H, q, *J*=7.1 Hz, C*H*Me), 7.3–7.9 (3H, m, 6-, 7-, 8-H), 8.23 (1H, d, *J*=8.0 Hz, 5-H), 8.31 (2H, br s, NH_2). Anal. calcd for $C_{10}H_{10}N_3OBr$: C, 44.80; H, 3.76; N, 15.67; Br, 29.80. Found C, 44.67; H, 3.72; N, 15.62; Br, 29.82.

2-[1-(Phenylhydrazono)ethyl]-3-amino-4(3*H*)-quinazolinone (5). To a solution of 2-(1-bromethyl)-3-amino-4(3*H*)-quinazolinone **4** (2.6 g, 10 mmol) in ethanol (5 ml) was added phenylhydrazine (1.81 ml, 2 g, 20 mmol). The reaction mixture was refluxed for 4 h. After cooling of the mixture, the crystallized product was filtered off, washed with cold ethanol, dried and recrystallized from ethanol, to give 2.37 g (81%) of compound **5** as a yellow solid, mp. 205–207°C. $UV_{(EtOH)}$ λ_{max}(log ϵ): 226 (4.34), 298 (3.97), 356 (4.23); $IR_{(KBr)}$ ν_{max}: 3304, 1660, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.32 (3H, s, =CMe) 6.5–7.8 (8H, m, quinazolone 6-, 7-, 8-H and Ph), 6.77 (1.24H, s, $NNH_{2\text{-}Z}$), 8.18 (1H, d, *J*=8.0 Hz, 5-H) 8.21 (0.38H, s, =NNH_{E1}Ph), 13.35 (0.76H, s, $NNH_{2\text{-}E1}$).14.39 (0.62H, s, =NNH_ZPh); (DMSO-d_6): 2.36 (3H, s, =CMe), 6.5–7.8 (8H, m, quinazolone 6-, 7-, 8-H and Ph), 8.21 (1H, d, *J*=8.0 Hz, 5-H), 8.31 (0.12H, s, $NNH_{2\text{-}Z}$), 8.65 (1.40H, s, =$NNH_{2\text{-}E2}$), 10.11 (0.24H, s, =NNH_{E1}Ph), 11.85 (0.70H, s, NNH_{E2}-Ph).12.90 (0.48H, s, =NNH_{E1}Ph),14.23 (0.06H, s, =NNH_ZPh). Anal. calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.16; N, 23.87;. Found C, 65.64; H, 5.12; N, 23.76.

2-(2-Indolyl)-3-amino-4(3*H*)-quinazolinone (6). 2-(1-Phenyl-hydrazonoethyl)-3-amino-4(3*H*)-quinazolinone **5**

(2 g, 10 mmol) was gradually added to preheated 85% phosphoric acid (25 ml) at 180–185°C. The reaction mixture was heated for 30 min, then cooled to ambient temperature, and diluted with water (100 ml). The precipitated product was filtered off and dissolved in chloroform (30 ml). The chloroformic solution was filtered, and treated with 5% aqueous sodium hydroxide (2×15 ml), and then with water (2×15 ml). The dried (sodium sulfate) organic solution was evaporated to dryness in vacuo, and the residue was recrystallized from ethanol, to give 2.3 g (85%) of compound **6** as pale-yellow crystals, mp 213–215°C (lit. mp[30] 214–216°C). $IR_{(KBr)}$ ν_{max}: 3400, 3210, 1660, 1670, 1570 cm^{-1}; ^1H NMR ($CDCl_3$):6.10 (2H, s, NNH_2), 6.8–8.0 (8H, indol 3-, 4-, 5-, 6-, 7-H and quinazolone 6-, 7-, 8-H), 8.30 (1H, d, J=8.0 Hz, quinazolone 5-H) 8.31 (1H, s, indol NH).). Anal. calcd for $C_{16}H_{12}N_4O$: C, 69.56; H, 4.38; N, 20.28;. Found C, 69,38; H, 4.42; N,20. 95.

2-(2-Indol-2-yl)-3-benzylideneamino-4(3*H*)-quinazolinone (7). To a solution of 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6** (207 mg, 1 mmol) in dimethylformamide (0.5 ml) was added benzaldehyde (0.19 ml, 0.2 g, 2 mmol). The mixture was stirred for 4 h at room temperature. Following dilution of the dark reaction mixture with 2-propanol, the precipitated yellow product was filtered off and washed with 2-propanol, to give 206 mg (71%) of compound **7** as a yellow solid, mp 198–202°C. $UV_{(EtOH)}$ λ_{max}(log ϵ): 216 (4.42), 250 (4.37), 340 (4.34); $IR_{(KBr)}$ ν_{max}: 3230, 1670, 1610, 1575 cm^{-1}; ^1H NMR ($CDCl_3$): 6.5–7.8 (14H, m, Ar-H, indol NH), 7.98 (0.1H, s, N=CH_Z) and 8.21 (0.9H, s, N=CH_E), 8.28 (1H, d, J= 8.0 Hz, quinazolone 5-H). Anal. calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.42; N, 15.37; Found C, 75.77; H, 4.54; N, 15.49.

8-Alkyl-7,8-dihydro-7,13*H*-indolo[2′3′;3,4]pyridazino-[2,1-*b*]quinazolin-5-ones (2a,b). To a solution of 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6** (270 g, 1 mmol) in ethanol (5 ml) were added the appropriate aliphatic aldehyde (2 mmol) and one drop of conc. hydrochloric acid. The mixture was stirred for 5 h at 80°C, and then evaporated to dryness. The solid residue was crystallized from 2-propanol to give **2a**,**b** as pale-yellow crystals (Table 1).

8-Aralkyl and 8-aryl-7,8-dihydro-7,13*H*-indolo[2′3′;3,4]-pyridazino[2,1-*b*]quinazolin-5-ones (2c–u). To a well-homogenized mixture of 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6** (270 g, 1 mmol) and the appropriate araliphatic or (hetero)aromatic aldehyde (2 mmol) was added dimethylformamide (0.5 ml). The mixture was heated up to 140°C in an oil bath, and kept for 2 h at 140–150°C. After cooling, the product was crystallized from 2-propanol, then filtered off and washed with cold 2-propanol to give **2c–u** as pale-yellow crystals (Table 1).

7,13*H*-Indolo[2′3′;3,4]pyridazino[2,1-*b*]quinazolin-5-one (8). (a) To a solution of 2-(2-indolyl)-3-amino-4(3*H*)-quinazolinone **6** (207 mg, 1 mmol) in dimethylformamide (0.5 ml), phosphoryl chloride (150 mg, 1 mmol) was added at 0–5°C. The mixture was stirred for 2 h at 55°C, then cooled and diluted with water. The precipitated crystals were filtered off, washed with water and recrystallized from ethanol, to give 230 mg (85%) of **8** as yellow crystals, mp 316°C.

(b) A solution of 2-(2-indolyl)-3-amino-3*H*-quinazolin-4-one **6** (207 mg, 1 mmol) in formic acid (4 ml) was stirred for 6 h at 120°C. After cooling, the solution was diluted with water. The precipitated crystals were filtered off, washed with water and recrystallized from ethanol to give 210 mg (77%) of **8** as a yellow solid, mp 314°C. $UV_{(EtOH)}$ λ_{max} (log ϵ): 218 (4.46), 274 (4.32), 284 (4.33), 296 (4.36), 308 (4.39), 332 (4.37), 350 (4.35), 368 (4.28); $IR_{(KBr)}$ ν_{max}: 3400, 1690, 1575 cm^{-1}; ^1H NMR ($CDCl_3$): 7.15–7.8 (8H, m, 1-, 2-, 3-, 9-, 10-, 11-, 12-H, N(13)H), 8.28 (1H, d, J=8.2 Hz, 4-H), 8.41 (1H, s, 8-H). Anal. calcd for $C_{17}H_{10}N_4O$: C, 71.32; H, 3.52; N, 19.57; Found C, 71.37; H, 3.54; N, 19.49.

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