NITROGEN BRIDGEHEAD COMPOUNDS PART 90.[1] AN EFFICIENT VERSATILE SYNTHESIS OF 1-METHYL-2-SUBSTITUTED 1,2,3,4-TETRAHYDRO-6*H*-PYRAZINO[2,1-*b*]QUINAZOLINE-3,6-DIONES

József Kökösi[a]*, János Almási[a], Benjamin Podányi,[b] Miklós Fehér,[b] Zsolt Böcskei,[b] Kálmán Simon,[b] and István Hermecz[b]*

[a]Institute for Pharmaceutical Chemistry Semmelweis University of Medicine, Högyes E. u. 9. 1092 Budapest, Hungary

[b]Department of Chemical Research, Chinoin Pharmaceutical and Chemical Works Ltd, POB 110, 1325 Budapest, Hungary

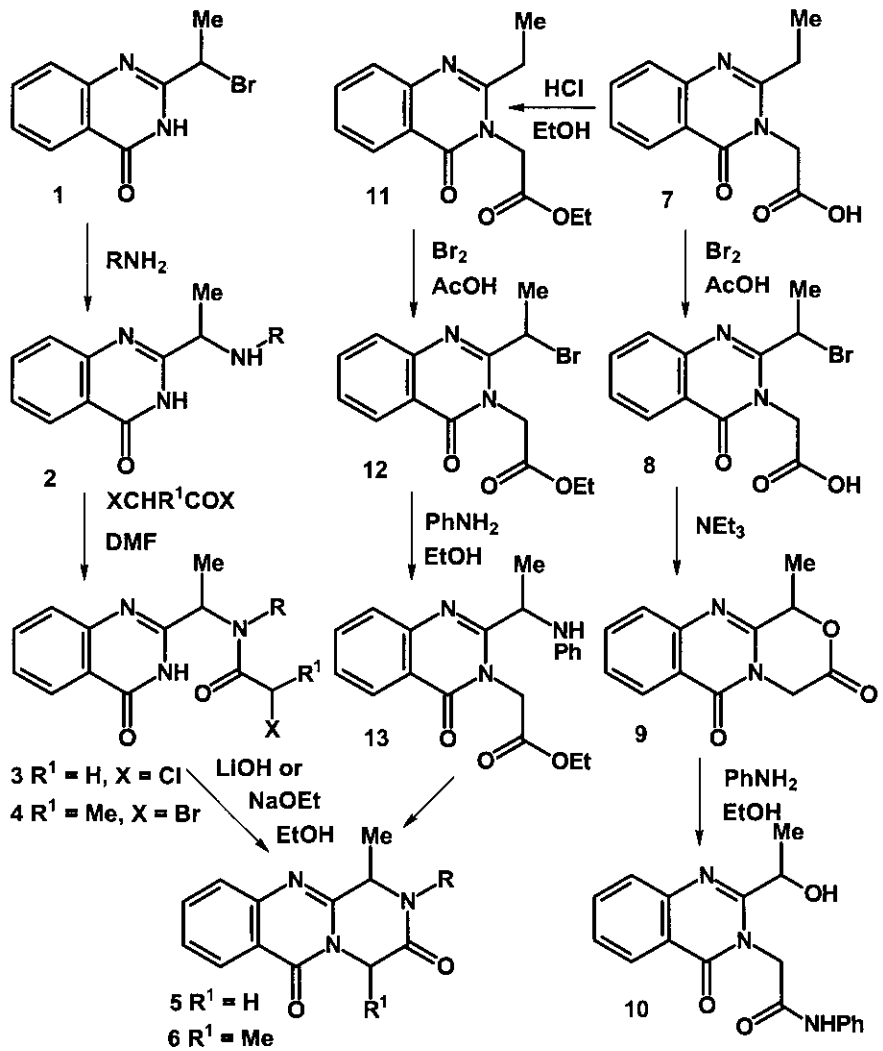
Abstract - A versatile synthesis of 2-substituted 1-methyl- and 1,4-dimethyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones is presented, starting from 2-(1-bromoethyl)quinazolin-4(3*H*)-one. The key step of the reaction sequence is the diastereoselective cyclization of 2-{[1-(*N*-2-haloacyl-*N*-substituted amino]ethyl}quinazolin-4(3*H*)-ones. Usually 1,4-dimethyl derivatives are obtained as pure racemic *cis*-compounds (2-alkyl and 2-benzyl derivatives), or a mixture of diastereomers, containing the 4-methyl group in quasiaxial position.

INTRODUCTION

The diverse biological activities of heterocondensed quinazolines have contributed to extensive efforts directed towards syntheses of novel members of these ring systems.[2-4] Pyrazino[2,1-*b*]quinazoline-3,6-diones are known to exhibit sedative, hypnotic and tranquilizing activities.[5] They are formally anthranoylcyclodipeptides having conformationally restricted structures, which as rigid spacers became a focus of increased attention in studies of stabilization of specific backbone conformations.[6]

Recently several alkaloids containing pyrazino[2,1-*b*]quinazoline-3,6-dione structural moiety have been isolated from *Aspergillus* species.[7, 8] They have received increasing interest due to their biological activity. Among them valuable pharmacons are found: spiroquinazolone alkaloid of *Aspergillus flavipes*,[7] the structurally related alkaloid fumiquinazolone (isolated from marine fungus *Aspergillus fumigatus*[9]) having Substance P inhibitory activity[10] on human neurokinin-1 receptors, and furthermore a new hexacyclic alkaloid metabolite of *Aspergillus fisherii*, which has been claimed as antineoplastic enhancer.[11]

Synthesis of pyrazino[2,1-*b*]quinazolines was achieved by oxidative cyclization of *o*-aminobenzylpiperazine[12] and 1-(*o*-azidobenzoyl)-2,5-piperazinediones,[13] by deprotection of 2-(peptidoamino)benzophenones,[14] their derivatives,[15] and *N*-substituted anthranilic acids.[16] 2-Methyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-b]quinazoline-3,6-diones and other 2-substituted derivatives were prepared by cyclocondensation of anthranilic acid with 5-ethoxy-1-methyl-1,2,3,6-tetrahydropirazin-2-ones,[17,18] and by cyclization of 2-[*N*-(2-chloroacetyl)-*N*-arylamino]methylquinazolin-4(3*H*)-ones,[19] respectively.



We extended Reddy's approach[19] to the preparation of 1-methyl and 1,4-dimethyl derivatives of pyrazino[2,1-*b*]quinazoline-3,6-diones containing different substituent at position 2.

SYNTHESIS

Reactions of 2-(1-bromoethyl)quinazolin-4(3*H*)-one[20] (**1**) with 2.5 mole equiv. of primary amines readily gave the appropriate 2-(1-aminoethyl)quinazolones (**2**) either in boiling ethanol (Method A, in the case of

alkyl- and aralkylamines) or in *N,N*-dimethylformamide at 100 °C (Method B, in the case of anilines). When 2-(1-arylaminoethyl)quinazolin-4(3*H*)-ones (**2h-q**) were prepared, the reaction time depends upon the electronic property of the substituent of anilines. Thus, the reaction with anilines which have pK_a values of about 5, required 4 to 6 hours for completion, but anilines with lower pK_a required longer reaction period. For example, *p*-nitroaniline, which has pK_a value of 1, gave only 3% of the product (**2q**) after ninety hours.

Table 1. 2-(1-Aminoethyl)quinazolin-4(3*H*)-ones (**2**).

Compd No	R	Method	Reaction time (h)	Reaction temp °C	Yield %	mp °C	Recrystall solvent	Formula
2a	H	A	72	20	45	180-182	2-PrOH	$C_{10}H_{11}N_3O$
2b	Me	A	60	20	86	153-155	Et_2O	$C_{11}H_{13}N_3O$
2c	Et	A	24	20	77	99-101	Hexane	$C_{12}H_{15}N_3O$
2d	*n*-Pr	A	4	50	77	81-83	Hexane	$C_{13}H_{17}N_3O$
2e	*n*-Bu	A	6	80	75	75-77	Hexane	$C_{14}H_{19}N_3O$
2f	$PhCH_2$	A	5	90	79	117-119	Et_2O	$C_{17}H_{17}N_3O$
2g	$PhCH_2CH_2$	A	12	90	68	82-85	Hexane	$C_{18}H_{19}N_3O$
2h	Ph	B	5	100	94	215-218	EtOH	$C_{16}H_{15}N_3O$
2i	*p*-MeOPh	B	3	100	71	196-198	EtOH	$C_{17}H_{17}N_3O_2$
2j	*p*-MePh	B	4	100	89	203-206	EtOH	$C_{17}H_{17}N_3O$
2k	*p*-FPh	B	6	100	87	202-204	EtOH	$C_{16}H_{14}N_3OF$
2l	*p*-ClPh	B	6	100	79	217-222	EtOH	$C_{16}H_{14}N_3OCl$
2m	*p*-EtOPh	B	4	100	90	198-201	EtOH	$C_{18}H_{19}N_3O_2$
2n	*p*-NCPh	B	12	100	48	246-250	EtOH	$C_{17}H_{14}N_4O$
2o	*p*-CF_3Ph	B	9	100	69	199-203	EtOH	$C_{17}H_{14}N_3OF_3$
2p	*p*-AcPh	B	72	110	83	205-208	EtOH	$C_{18}H_{17}N_3O_2$
2q	*p*-NO_2Ph	B	90	110	3	242-244	EtOH	$C_{16}H_{14}N_4O_3$

The side chain amino group of 2-(1-aminoethyl)quinazolin-4(3*H*)-ones (**2**) underwent *N*-acylation on treatment with chloroacetyl chloride and 2-bromopropionyl bromide to yield compounds (**3**) and (**4**), respectively. According to the ^{1}H-NMR spectra of compounds (**4**) these derivatives were formed as diastereomeric mixtures. *N*-Alkyl and *N*-benzyl derivatives (**2a-f**) were acylated in $CHCl_3$ in presence of one equiv. of pyridine, as a proton acceptor (Method C). In the case of the arylamino derivatives (**2h-m**) and (**2p**) reactions were carried out in *N,N*-dimethylformamide (Method D).

The 2-{1-[(2-halogenoacyl)amino]ethyl}quinazolin-4(3*H*)-ones (**3**) and (**4**) readily cyclised under basic conditions to pyrazino[2,1-*b*]quinazoline-3,6-diones (**5**) and (**6**) using one mole equiv. of sodium ethoxide (R^1 = H) or lithium hydroxide (R^1 = Me) in boiling ethanol (Method E).

We also investigated alternative synthetic routes for 2-phenyl derivative of pyrazino[2,1-*b*]quinazolin-3,6-dione (**5h**), starting from 2-ethyl-4-oxo-3,4-dihydroquinazoline-3-acetic acid (**7**), prepared from 2-ethyl-4*H*-[3,1]benzoxazin-4-one[21] with glycine in boiling acetic acid. The ethyl ester (**11**) was prepared both from **7** by esterification (Method F), and from 2-ethylquinazolin-4(3*H*)-one[22] by *N*-alkylation with ethyl

chloroacetate in ethanol in the presence of sodium ethoxide (Method G) in 85 and 67% yields, respectively.

2-Ethyl-4-oxo-3,4-dihydroquinazoline-3-acetic acid (**7**), and its ethyl ester (**11**) were brominated with one mol equiv. of bromine in acetic acid in the presence of sodium acetate to afford bromo derivatives (**8**) and (**12**), respectively.

Reaction of 2-(1-bromoethyl)-4-oxo-3,4-dihydroquinazoline-3-acetic acid (**8**) with 2.5 mol equiv. of aniline in boiling ethanol gave 2-[2-(1-hydroxyethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetanilide (**10**) probably *via* 3,4-dihydro-1*H*,7*H*-[1,4]oxazino[3,4-*b*]quinazoline-3,6-dione (**9**). 3,4-Dihydro-1*H*,7*H*-[1,4]-oxazino[3,4-*b*]quinazoline-3,6-dione (**9**) could be isolated when 2-(1-bromoethyl)-4-oxo-3,4-dihydro-quinazoline-3-acetic acid (**8**) was cyclized on the action of triethylamine in $CHCl_3$ at ambient temperature. Reaction of [1,4]oxazino[3,4-*b*]quinazoline-3,6-dione (**9**) with aniline in boiling ethanol afforded a ring-

Table 2. 2-[1-(Acylamino)ethyl]quinazolin-4(3*H*)-ones (**3**) and (**4**).

Compd No	R	Method	Yield %	mp °C	Recrystall solvent	Formula
3a	H	C	60	217-219	EtOH	$C_{12}H_{12}N_3O_2Cl$
3b	Me	C	51	124-129	EtOH	$C_{13}H_{14}N_3O_2Cl$
3c	Et	C	64	149-150	CH_2Cl_2	$C_{14}H_{16}N_3O_2Cl$
3d	*n*-Pr	C	36	126-128	2-PrOH	$C_{15}H_{18}N_3O_2Cl$
3e	*n*-Bu	C	52	70-72	2-PrOH	$C_{16}H_{20}N_3O_2Cl$
3f	$PhCH_2$	C	71	128-131	EtOAc	$C_{19}H_{18}N_3O_2Cl$
3h	Ph	D	85	180-186	H_2O	$C_{18}H_{16}N_3O_2Cl$
3i	*p*-MeOPh	D	87	174-178	EtOH	$C_{19}H_{18}N_3O_3Cl$
3j	*p*-MePh	D	78	191-192	EtOH	$C_{19}H_{18}N_3O_2Cl$
3k	*p*-FPh	D	82	174-176	EtOH	$C_{18}H_{15}N_3O_2ClF$
3l	*p*-ClPh	D	73	198-200	DMF/H_2O	$C_{18}H_{15}N_3O_2Cl_2$
3m	*p*-EtOPh	D	79	177-179	EtOH	$C_{20}H_{20}N_3O_3Cl$
3p	*p*-AcPh	D	80	219-223	DMF/H_2O	$C_{20}H_{18}N_3O_3Cl$
4b	Me	C	81	150-151	Et_2O	$C_{14}H_{16}N_3O_2Br$
4c	Et	C	88	118-122	Et_2O	$C_{15}H_{18}N_3O_2Br$
4d	*n*-Pr	C	57	128-134	Et_2O	$C_{16}H_{20}N_3O_2Br$
4e	*n*-Bu	C	65	119-122	Et_2O	$C_{17}H_{22}N_3O_2Br$
4f	$PhCH_2$	C	65	125-130	Et_2O	$C_{20}H_{20}N_3O_2Br$
4h	Ph	D	62	205-207	2-PrOH	$C_{19}H_{18}N_3O_2Br$
4i	*p*-MeOPh	D	80	158-163	2-PrOH	$C_{20}H_{20}N_3O_3Br$
4k	*p*-FPh	D	72	175-179	2-PrOH	$C_{19}H_{17}N_3O_2BrF$
4m	*p*-EtOPh	D	71	139-149	2-PrOH	$C_{21}H_{22}N_3O_3Br$
4p	*p*-AcPh	D	73	181-183	EtOH	$C_{21}H_{20}N_3O_3Br$

opened product (**10**) instead of the expected 3*H*,6*H*-[1,4]pyrazino[3,4-*b*]quinazoline-3,6-dione (**5h**). The latter compound was obtained from ethyl 2-[2-(1-bromoethyl)-4-oxo-3,4-dihydroquinazolin-3-yl}acetate (**12**) in two steps. Compound (**12**) reacted first with aniline in boiling ethanol and the 2-[1-

(phenylamino)ethyl] derivative (**13**) was heated in boiling toluene to give 2-phenyl derivative of [1,4]pyrazino[3,4-*b*]quinazoline-3,6-dione (**5h**).

Table 3. 1*H*,7*H*-pyrazino[3,4-*b*]quinazoline-3,6-diones (**5**) (R^1 = H) and (**6**) (R^1 = Me).

Compd No	R	Yield %	mp °C	Recrystall solvent	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
5a	H	88	178-182	H_2O	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33	62.98	4.65	18.67
5b	Me	74	175-177	Et_2O	$C_{13}H_{13}N_3O_2$	64.19	5.39	17.27	64.08	5.41	17.25
5c	Et	76	178-179	Et_2O	$C_{14}H_{15}N_3O_2$	65.36	5.88	16.33	65.48	6.01	16.27
5d	*n*-Pr	57	138-139	Et_2O	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49	66.54	6.28	15.40
5e	*n*-Bu	89	oil		$C_{16}H_{19}N_3O_2$	67.35	6.71	14.73	67.36	6.82	14.53
5f	$PhCH_2$	59	154-155	EtOH	$C_{19}H_{17}N_3O_2$	71.46	5.37	13.16	71.36	5.18	12.98
5h	Ph	85	217-218	EtOH	$C_{18}H_{15}N_3O_2$	70.81	4.95	13.76	70.95	5.04	13.82
5i	*p*-MeOPh	82	143-147	2-PrOH	$C_{19}H_{17}N_3O_3$	68.05	5.11	12.53	67.84	5.14	12.55
5j	*p*-MePh	77	163-166	2-PrOH	$C_{19}H_{17}N_3O_2$	71.46	5.37	13.16	71.33	5.44	13.26
5k	*p*-FPh	46	199-203	2-PrOH	$C_{18}H_{14}N_3O_2F$	66.87	4.36	9.90	66.89	4.15	10.09
5l	*p*-ClPh	61	220-223	EtOH	$C_{18}H_{14}N_3O_2Cl$	63.63	4.15	12.37	63.54	4.04	12.44
5m	*p*-EtOPh	76	173-175	EtOH	$C_{20}H_{19}N_3O_3$	68.75	5.48	12.03	68.67	5.54	11.84
6b	Me	81	184-185	Et_2O	$C_{14}H_{15}N_3O_2$	65.36	5.88	16.33	65.58	5.96	16.54
6c	Et	89	129-132	Et_2O	$C_{15}H_{17}N_3O_2$	66.40	6.32	15.49	66.28	6.48	15.68
6d	*n*-Pr	86	118-122	Et_2O	$C_{16}H_{19}N_3O_2$	67.35	6.71	14.73	67.21	6.80	14.72
6e	*n*-Bu	88	oil		$C_{17}H_{21}N_3O_2$	68.20	7.07	14.04	68.03	7.11	13.79
6f	$PhCH_2$	79	179-181	2-PrOH	$C_{20}H_{19}N_3O_2$	72.05	5.74	12.60	72.16	5.63	12.55
6h	Ph	98	215-218	2-PrOH	$C_{19}H_{17}N_3O_2$	71.46	5.37	13.16	71.34	5.46	13.27
6i	*p*-MeOPh	66	187-189	2-PrOH	$C_{20}H_{19}N_3O_3$	68.75	5.48	12.03	68.88	5.61	11.95
6k	*p*-FPh	73	183-185	2-PrOH	$C_{19}H_{16}N_3O_2F$	67.65	4.78	12.46	67.78	4.81	12.31
6m	*p*-EtOPh	84	194-196	2-PrOH	$C_{21}H_{21}N_3O_3$	69.41	5.82	11.56	69.57	5.78	11.73

SPECTROSCOPIC INVESTIGATION

Some characteristic ^{1}H NMR data are tabulated in Tables 4-6. ^{13}C NMR data on 1,4-dimethyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**6c**, **m**) are collected in Table 6. The crosspeaks at the NOESY spectra of compounds (**6f**) and (**6m**) are listed in Table 7. Solid state structure of compound (**6f**) was determined by X-ray investigations (Tables 8 and 9, Figure 1).

Earlier it was determined that 2,4-dimethyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**14**) adopted conformation (**15A**, R = R^1 = Me, R^2 = R^3 = H) both in solid state[23] and in solution,[17] where pyrazinone ring had a flattened boat conformation and methyl group occupied quasiaxial position to avoid 1-3 allylic strain,[24-28] which would be present in the alternative conformation (**15B**, R = R^1 = Me, R^2 = R^3 = H). The signal of equatorial 4-H proton of compound (**14**) appeared as a quartet centered at 5.39 ppm in $CDCl_3$ (and at 5.14 ppm in DMSO-d_6), due to the anisotropic effect of the adjacent carbonyl group at position 6.

X-Ray investigations[29] of a single crystal of compound (**6f**) indicated the presence of a similar conformation (**15A**) to that of 2,4-dimethyl derivative (**14**), and the presence of 1,4-*cis* isomer (**15A**, R =

Table 4. ^{1}H NMR Data on Selected Compounds (**2**, **3**) in $CDCl_3$ (ppm).

Compd	Me[a]	CH[a]	R	Ar-$H_{6,7,8}$	Ar-H_5	CONH	Others
2b	1.49 (3H, d)	3.77 (1H, q)	2.45 (3H, s, Me)	7.35-7.78 (3H, m)	8.28 (1H, m)	10.40 br	
2c	1.50 (3H, d)	3.86 (1H, q)	1.15 (3H, t, *J*~6.9 Hz, Me), 2.40-2.80 (2H, q, *J*~6.9 Hz, NCH_2)	7.20-7.90 (3H, m)	8.25 (1H, m)	10.35 br	
2d	1.70 (3H, d)	3.79 (1H, q)	0.93 (3H, t, *J*~6.9 Hz, Me), 1.27-1.75 (2H, m, CH_2), 2.58 (2H, t, *J*~6.5 Hz, NCH_2)	7.25-7.93 (3H, m)	8.31 (1H, m)	10.42 br	
2e	1.75 (3H, d)	3.88 (1H, q)	0.91 (3H, t, *J*~6.9 Hz, Me), 1.10-1.70 (4H, m, CH_2CH_2), 2.63 (2H, t, *J*~6.5 Hz, NCH_2)	7.30-7.90 (3H, m)	8.35 (1H, m)	10.60 br	
2f	1.50 (3H, d)	3.95 (1H, q)	3.80 (2H, s, NCH_2)	7.10-7.90 (8H, m)[b]	8.33 (1H, m)	10.50 br	
2g	1.44 (3H, d)	3.86 (1H, q)	2.88 (4H, m, NCH_2CH_2)	7.11-7.90 (8H, m)[b]	8.31 (1H, m)	10.65 br	
2h	1.67 (3H, d)	4.47 (1H, q)		6.50-7.90 (8H, m)[b]	8.22 (1H, m)	10.80 br	
3b	1.66 (3H, d)	5.63 (1H, q)	3.02 (3H, s, Me)	7.25-7.80 (3H, m)	8.33 (1H, m)	10.58 br	4.23 (2H, s, CH_2Cl)
3c	1.75 (3H, d)	5.30 (1H, q)	1.31(3H, t, *J*~6.9 Hz, Me), 3.60 (2H, q, *J*~6.9 Hz, NCH_2)	7.30-7.90 (3H, m)	8.33 (1H, m)	10.10 br	4.19 (2H, s, CH_2Cl)
3d	1.77 (3H, d)	5.12 (1H, q)	1.43 (3H, t, *J*~6.9 Hz, Me), 1.40-1.90 (2H, m, CH_2) 3.08 (2H, t, *J*~6.5 Hz, NCH_2)	7.30-7.90 (3H, m)	8.33 (1H, m)	12.06 br	4.16 (2H, s, CH_2Cl)
3h	1.66 (3H, d)	5.72 (1H, q)		6.50-7.90 (8H, m)[b]	8.33 (1H, m)	10.98 br	3.81 (2H, s, CH_2Cl)
3i	1.50 (3H, d)	5.67 (1H, q)	3.80 (3H, s, OMe)	6.80-7.90 (7H, m)[b]	8.33 (1H, m)	10.60 br	3.72 (2H, s, CH_2Cl)
3j[c]	1.19 (3H, d)	5.31 (1H, q)	2.33 (3H, s, Me)	7.20-7.90 (7H, m)[b]	8.12 (1H, m)	12.32 br	3.81 (2H, s, CH_2Cl)
3k[c]	1.25 (3H, d)	5.30 (1H, q)		7.25-7.90 (7H, m)[b]	8.12 (1H, m)	12.40 br	3.81 (2H, s, CH_2Cl)
3m[c]	1.26 (3H, d)	5.38 (1H, q)	1.31 (3H, t, *J*~7 Hz, Me) , 4.11 (2H, q, *J*~7 Hz, OCH_2)	6.80-7.90 (7H, m)[b]	8.12 (1H, m)	11.60 br	3.94 (2H, s, CH_2Cl)
3n[c]	1.55 (3H, d)	5.80 (1H, q)	2.41 (3H, s, COMe)	6.50-7.90 (7H, m)[b]	8.12 (1H, m)	12.25 br	3.28 (2H, s, CH_2Cl)

a: *J*~6.8 Hz; b: Ar-$H_{6,7,8}$ + protons of Ph or Ar; c: in DMSO-d_6;

Table 5. ^{1}H NMR Data on Selected Compounds (**5**) in $CDCl_3$ (ppm).

Compd	1-Me[a]	1-H[a]	2-R	Ar-$H_{8,9,10}$	Ar-H_7	4-H_{ax}[b]	4-H_{eq}[b]
5b	1.69 (3H, d)	4.90 (1H, q)	2.38 (3H, s, Me)	7.15-7.90 (3H, m)	8.33 (1H, m)	4.38 (1H, d)	5.40 (1H, d)
5c	1.62 (3H, d)	4.61 (1H, q)	1.38 (3H, t, *J*~6.5 Hz, Me), 3.21 and 3.90 (2H, dt, *J*~6 Hz, $^2J_{NCH_2}$~15 Hz, NCH_2)	7.30-7.90 (3H, m)	8.33 (1H, m)	4.18 (1H, d)	5.25 (1H, d)
5d	1.62 (3H, d)	4.58 (1H, q)	0.94 (3H, t, *J*~6.5 Hz, Me), 1.40-1.90 (2H, m, CH_2), 3.02 and 3.88 (2H, dt, *J*~6 Hz, $^2J_{NCH_2}$~15 Hz, NCH_2)	7.30-7.90 (3H, m)	8.30 (1H, m)	4.20 (1H, d)	5.27 (1H, d)
5f	1.51 (3H, d)	4.51 (1H, q)	4.35 and 5.13 (2H, d, $^2J_{NCH_2}$~15 Hz, NCH_2)	7.25-7.90 (8H, m)[c]	8.25 (1H, m)	4.20 (1H, d)	5.38 (1H, d)
5h	1.66 (3H, d)	4.51 (1H, q)		6.50-7.90 (8H, m)[c]	8.30 (1H, m)	4.80 (1H, d)	5.40 (1H, d)
5i	1.69 (3H, d)	4.90 (1H, q)	3.80 (3H, s, OMe)	6.70-7.90 (7H, m)[c]	8.30 (1H, m)	4.40 (1H, d)	5.40 (1H, d)
5j	1.69(3H, d)	4.90 (1H, q)	2.38 (3H, s, Me)	7.10-7.90 (7H, m)[c]	8.33 (1H, m)	4.38 (1H, d)	5.40 (1H, d)
5k	1.70 (3H, d)	4.88 (1H, q)		7.00-7.90 (7H, m)[c]	8.30 (1H, m)	4.39 (1H, d)	5.41 (1H, d)
5m	1.66 (3H, d)	4.90 (1H, q)	1.44 (3H, t, *J*~7 Hz, Me), 4.05 (2H, q, *J*~7 Hz, OCH_2)	6.90-7.90 (7H, m)[c]	8.30 (1H, m)	4.41 (1H, d)	5.41 (1H, d)

a: *J*~6.8 Hz; b: $^2J_{4\text{-}CH_2}$~ 18 Hz; c: Ar-$H_{8,9,10}$ + protons of Ph or Ar

Table 6. NMR Data on Selected Compounds (**6c**,**d**,**f**), (**6i**) and (**6m**) in DMSO-d_6 (δ, ppm)

	^{1}H-NMR							^{13}C-NMR			
Proton	**6c**-I[a] R = Et	**6d**-I[a] R = nPr	**6f**-I[a,b] R = CH_2Ph	**6i**-I[a] R = *p*MeOPh	**6i**-II[c]	**6m**-I[a] R = *p*EtOPh	**6m**-II[c]	Carbon	**6c**-I[a] R = Et	**6m**-I[a] R = *p*EtOPh	**6m**-II[c]
R^1	4.75q[d]	4.71q[d]	4.57q[d]	4.87q[d]	1.35d[d]	4.86q[d]	1.35d[d]	R^1	-	-	16.2
R^2	1.57d[d]	1.57t[d]	1.78d[d]	1.62d[d]	5.43q[d]	1.62d[d]	5.42q[d]	R^2	18.7	19.1	-
4-H	4.98q[d]	4.99q[d]	5.45q[d]	5.12q[d]	5.30q[d]	5.11q[d]	5.29q[d]	C-1	55.9	60.2	54.1
4-CH_3	1.62d[d]	1.62d[d]	1.78d[d]	1.70d[d]	1.64d[d]	1.70d[d]	1.64d[d]	C-3	165.7	166.0	168.3
7-H	8.14d[e]	8.14d[e]	8.28d[e]	8.20d[e]	8.20d[e]	8.19d[e]	8.19d[e]	C-4	51.8	52.1	52.1
8-H	7.54t[e]	7.54t[e]	7.48t[e]	7.57t[e]	7.57t[e]	7.58t[e]	7.58t[e]	4-CH_3	22.0	21.7	16.7
9-H	7.85t[e]	7.85t[e]	7.46t[e]	7.87t[e]	7.87t[e]	7.87t[e]	7.87t[e]	C-6	159.8	159.9	159.7
10-H	7.65d[e]	7.65t[e]	7.57d[e]	7.67d[e]	7.70d[e]	7.67d[e]	7.70d[e]	C-6*a*	120.0	120.2	120.1
								C-7	134.9	135.0	134.9
								C-8		127.0	127.5
								C-9		126.9	127.4
								C-10		126.4	126.4
								C-10*a*		152.4	152.2
								C-11*a*		147.5	147.0
R	3.76dq[f]	3.71m[g]	5.37d[h]	7.32d[h]	7.20d[h]	7.30d[h]	7.18d[h]	R	39.4	158.1	158.0
	3.19dq[f]	3.06m[g]	4.18d[h]	7.03d[h]	7.00d[h]	7.00d[h]	6.98d[h]		12.9	131.9	130.8
	1.13t[i]	1.58m	7.29m	3.80s	3.80s	4.04q[d]	4.04q[d]			129.3	130.4
		0.85t[d]				1.35t[d]	1.34t[d]			115.1	114.8
										63.5	63.4
										14.8	14.8

a: **15A** $R^1 = R^3 = Me$, $R^2 = H$; b: in $CDCl_3$; c: **15B** $R^1 = H$, $R^2 = R^3 = Me$; d: *J*~7.0 Hz; e: *J*~7.8 Hz; f: *J*~7.1 and 13.8 Hz; g: *J*~14.8 Hz; h: *J*~8.8 Hz; i: *J*~7.1 Hz;

CH_2Ph, $R^1 = R^3 = Me$, $R^2 = H$). Bond lengths and angles are in the expected regions (Table 8). Both C12 and C20 methyl groups are in pseudoaxial positions and piperazinone ring assumes a $^{C1,C4}B$ flattened boat *conformation*[30] in accordance with the double bond character of the N5-C11*a* and N2-C3 bonds (1.383 and 1.359 Å, respectively) (Figure 1a). The distortion is due to the close contacts of two hydrogen atoms of the methyl groups which are separated only by a distance of 2.22 Å. This is considerable less than the sum of the van der Waals radii of the two hydrogen atoms (2.4 Å). The structure of the compound in the solid state can be well described by three planes and the interplanar angles formed by them (Figure 1b). The first plane is formed by the quinazoline part of the tricycle and the attached atoms, the second by the C1, N2, C3, C4, C13 and O23 atoms forms an angle of 152.7(1) degrees with the first plane. The third plane is constituted by the benzyl moiety, which forms an interplanar angle of 103.1(1) degrees with the second and 75.8(1) degrees with the first plane.

The crosspeak observed between the two methyl groups in the NOESY spectrum of **6f** also supports the *cis*-isomeric structure and proves that the same conformation (**15A**, R = CH_2Ph, $R^1 = R^3 = Me$, $R^2 = H$) exists in solution as detected in solid state (Table 7). A further prove at this conformation is the chemical shift (5.45q) of 4-H due to the anisotropic effect of the C(6)=O group, characteristic for this spacial arrangement. The similar chemical shifts of 4-methyl and 4-H proton of other investigated 1,4-dimethyl derivatives (**6c,d** and **m**) to those of compounds (**6f**) and (**14**) indicated the quasiaxial position of 4-methyl group in these derivatives.

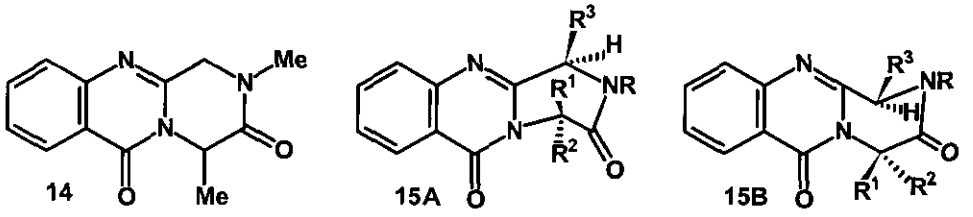
Table 7. Crosspeak of the NOESY Spectra of Compounds (**6f** and **6m**)

	crosspeak		
signal	**6f** (R = CH_2Ph)	**6m** (R = *p*-EtOPh)	
	isomer *cis*	*cis*	*trans*
1-H	1-CH_3 (s); N(2)CH_2 (w)	1-CH_3 (m); 2′-H (m)	1-CH_3 (s); 4-CH_3 (m); 2′-H (w)
4-H	4-CH_3 (s)	4-CH_3 (s)	4-CH_3 (s);
1-CH_3	1-H (s); N(2)CH_2 (m); 4-CH_3 (m)	1-H (m); 4-CH_3 (m)	1-H (s); 2′-H (m)
4-CH_3	4-H (s); 1-CH_3 (m)	4-H (s); 1-CH_3 (m)	1-H (m); 4-H (s)

(s) = strong, (m) = medium; (w) = weak

The 2-alkyl (**6c,d**) and 2-benzyl derivatives (**6f**) exist as pure *cis*-isomers, whereas 2-(*p*-ethoxyphenyl)-1,4-dimethyl derivative (**6m**) is a 1:2 mixture of *cis*- (**15A**, R = *p*-EtOPh, $R^1 = R^3 = Me$, $R^2 = H$) and *trans*-diastereomer (**15A**, R = *p*-EtOPh, $R^1 = H$, $R^2 = R^3 = Me$) according to the two sets of signals observed in the NMR spectrum of **6m**. A crosspeak was observed in the NOESY spectrum of **6m** between the two methyl groups in the minor set of signals proving that the minor compound of the mixture is the *cis*-isomer, and its conformation corresponds to structure (**15A**, R = *p*-EtOPh, $R^1 = R^3 = Me$, $R^2 = H$). A crosspeak was observed between 1-H and 4-Me in the major set of signals proving that the major component of the mixture is the *trans*-isomer, and its conformation correspond to structure **15B** (R = *p*-

EtOPh, R^1 = H, R^2 = R^3 = Me) (Table 7). Two sets of signals with similar chemical shifts to **6m** were observed in the ^{1}H NMR spectrum of **6i**, however the *cis/trans* ratio was 7:3. In the presence of NaOH the 1-H of the *trans*-isomer of **6i** exchanged fully with deuterium in 6 min, while the 4-H of this isomer and the 1-H and 4-H at the *cis*-isomer were completly deutereted only after 150 min. The ratio of the isomers also changed by the time, and a *cis/trans* equilibrium ratio of 8:1 from 7:3 was reached in one day at ambient temperature. Dissolving 2-ethyl-1,4-dimethyl derivative (**6c**) in D_2O-DCl and $CDCl_3$-D_2O no deuterium exchange was observed. However, when compound (**6c**) was dissolved in CH_3OD-NaOD protons in positions 1 and 4 were exchanged for deuterium in 75% and 100% after 20 min and 1 day, respectively.



At the 1-methyl derivatives (**5**) 4-CH_2 protons form an AB quartet (^2J = 18Hz) at 4.18-4.80 ppm and 5.25-5.41 ppm, furthermore the downfield shift of 1-methyl protons and the upfield shift of 1-H proton, compared with the respective signals of the diastereomers of **6m**, indicate the predominant conformer (**15A**, R^3 = Me, R^1 = R^2 = H) containing the 1-methyl group in quasiaxial position.

DISCUSSION

In the case of 2-alkyl and 2-benzyl derivatives of 1,4-dimethyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (**6b-f**) only the formations of one diastereomers were experienced, in spite of the starting compounds (**4b-f**) were a mixture of the diastereomers. Therefore it is assumed that under the basic cyclization conditions the thermodynamically less stable *trans*-1,4-dimethyl diastereomers (**15B**, R = alkyl, CH_2Ph, R^1 = H, R^2 = R^3 = Me) epimerized into the *cis*-diastereomers (**15A**, R = alkyl, CH_2Ph, R^1 = R^3 = Me, R^2 = H).

Quantum chemical calculations (AM1) show that in the case of 2-benzyl-1,4-dimethyl derivative (**6f**) the *cis*-diastereomer (**15A**, R = CH_2Ph, R^1 = R^3 = Me, R^2 = H) is at least 3.3 kcal/mol more stable than the *trans*-1,4-dimethyl diastereomer (**15B**, R = CH_2Ph, R^1 = H, R^2 = R^3 = Me). Similar calculations for 2-benzyl-1-methyl derivative (**5f**) indicate that conformer (**15A**, R = CH_2Ph, R^1 = R^2 = H, R^3 = Me), containing the methyl group in quasi-axial position is 2.5 kcal/mol more favorable then the alternative conformation, containing the methyl group in quasi-equatorial position. The calculated energy (PM3) of the *cis*-isomer of **6h** was found to be lower with about 4 kcal/mol than two value of the *trans* structure.

The semiempirical quantum chemical calculations suggest that the *cis*-isomers of compounds (**6**) are more stable than the *trans*-isomers. This is supported by the experimental data: in most cases the *cis*-isomer was formed and where the *trans*-isomer was also isolated its isomerisation towards the more stable *cis*-form was observed in NMR tube under basic conditions.

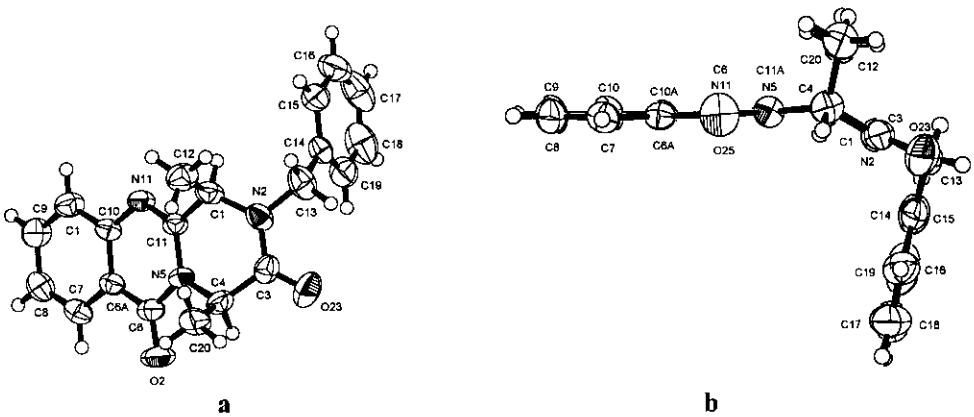


Figure 1: a) An ORTEP drawing of **6f** in a view which allows to see all atoms of the molecule.

b) This view of **6f** was obtained from a) by positioning C10, N11, C1 atoms just underneath C7, C6 and C4 and aligning at the same time the quinazoline moiety parallel with the horizontal axis of the picture. The figure nicely demonstrates the relation of the three main planes of the molecule.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Yields were not maximized. The UV spectra were recorded in ethanol with UNICAM SP-800, the IR spectra were recorded with a PYE UNICAM SP-1100 IR apparatus in potassium bromide disk. The ^{1}H NMR spectra were registered in $CDCl_3$ on a Bruker WP-80 (80 MHz) and on a Bruker DRX-400 (400 MHz) equipment (TMS was used as internal standard). ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument at 100 MHz. The NOESY spectra were recorded on a Bruker DRX-400 instrument using the standard microprogram of the XWINNMR (Bruker) software, applying 700 ms mixing time. Elementary analyses were performed with Perkin Elmer 2400 CHN Analyzer.

2-[1-(Substituted amino)ethyl]quinazolin-4(3*H*)-ones (2).

Method A: To a suspension of 2-(1-bromoethyl)quinazolin-4(3*H*)-one[20] (**1**) (10 g, 40 mol) in EtOH (50 mL), was added alkyl- or aralkylamine (100 mmol) and refluxed on a water bath. The reaction mixture was evaporated in vacuo to dryness. The residue was dissolved in $CHCl_3$ (100 mL), and washed with saturated Na_2CO_3 and brine. The dried (over $MgSO_4$) organic phase was evaporated and the residue was crystallized from the appropriate solvent to give **2** (see Tables 1 and 10).

Method B: To a solution of 2-(1-bromoethyl)quinazolin-4(3*H*)-one[20] (**1**) (10 g, 40 mmol) in *N,N*-dimethylformamide (50 mL), was added substituted aniline (100 mmol) and heated at 100 °C on a water bath. The reaction time was determined by TLC investigation. Then the reaction mixture was diluted with water and the precipitated crystals were filtered off, washed with water, dried and recrystallized from the appropriate solvent to give **2** (see Tables 1 and 10).

Table 8. Selected bond lengths [Å] and torsion angles [deg] for **6f**.

Bond length		Torsion angle	
N(11)-C(11*a*)	1.279(4)	C(3)-N(2)-C(1)-C(11*a*)	-30.6(5)
N(11)-C(10*a*)	1.382(4)	N(5)-C(11*a*)-C(1)-N(2)	28.6(4)
N(2)-C(3)	1.359(5)	C(1)-N(2)-C(3)-C(4)	1.5(5)
N(2)-C(1)	1.457(5)	C(11a)-N(5)-C(4)-C(3)	-30.7(4)
N(2)-C(13)	1.470(5)	N(2)-C(3)-C(4)-N(5)	29.2(5)
N(5)-C(11*a*)	1.383(4)	C(1)-N(2)-C(13)-C(14)	-71.6(6)
N(5)-C(6)	1.395(4)	N(2)-C(13)-C(14)-C(15)	115.3(4)
N(5)-C(4)	1.468(4)	C(4)-N(5)-C(11*a*)-C(1)	1.4(4)
C(3)-C(4)	1.507(5)	C(6)-N(5)-C(4)-C(20)	-82.5(4)
C(13)-C(14)	1.468(4)	N(11)-C(11*a*)-C(1)-C(12)	78.5(4)
A few irregular torsion angles [deg] (between chemically non-bounded atoms) which are important as far as the architecture of the molecule is concerned			
C(20)-C(4)···C(6)-O(25)	-74.5	C(12)-C(1)···C(10)-H(10)	69.0
H(4)-C(4)···C(6)-O(25)	30.5	H(1)-C(1)···C(10-H(10)	-36.0

2-{[1-(*N*-2-Haloacyl-*N*-substituted amino]ethyl}quinazolin-4(3*H*)-ones (3 and 4).

Method C: To a solution of 2-[1-(substituted amino)ethyl]quinazolin-4(3*H*)-one (**2**) (2.5 mmol) in $CHCl_3$ (10 mL) was added dropwise chloroacetyl chloride (0.32 g, 2.8 mmol) or 2-bromopropionyl bromide (0.56 g, 2.8 mmol) in the presence of mol equiv. of pyridine (0.26 g, 2.8 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at 25 °C for another 2 h. The solution was diluted with $CHCl_3$ (20 mL) and washed with saturated Na_2CO_3 and brine. The dried (over $MgSO_4$) organic phase was evaporated in vacuo to dryness and the residue was crystallized from the appropriate solvent to give **3** and **4** (see Tables 2 and 10).

Method D: To a solution of 2-[1-(substituted amino)ethyl]quinazolin-4(3*H*)-one (**2**) (2.5 mmol) in DMF (5 mL) was added dropwise chloroacetyl chloride (0.32 g, 2.8 mmol) or 2-bromopropionyl bromide (0.56 g, 2.8 mmol). The mixture was stirred at 0 °C for 1 h and at 25 °C for other 2 h. The reaction mixture was diluted with ice-water (25 mL). The precipitated crystals were filtered off, washed with water, dried and recrystallized from the appropriate solvent to give **3** and **4** (see Tables 2 and 10).

Ring Closure of 2-[1-(*N*-2-Haloacyl-*N*-substituted amino)ethyl]quinazolin-4(3*H*)-ones (3 and 4).

Method E: A solution of 2-[1-(*N*-2-haloacyl-*N*-substituted amino)ethyl]quinazolin-4(3*H*)-one (**3**) or (**4**) (10 mmol) and sodium ethoxide (R^1 = H) or lithium hydroxide (R^1 = Me) (12 mmol) in EtOH (25 mL)

was refluxed for 6 h. The mixture was neutralized with acetic acid and evaporated in vacuo to dryness. The residue was taken up in $CHCl_3$ (100 mL) and washed with saturated Na_2CO_3 solution and water (3 x 15 mL and 2 x 10 mL). The combined and dried organic phase was evaporated in vacuo to dryness. The residue was recrystallized from the appropriate solvent to give **5** and **6** (see Table 3).

2-(2-Ethyl-4-oxo-3,4-dihydroquinazolin-3-yl)acetic acid (7). A solution of 2-ethyl-4*H*-[3,1]benzoxazin-4-one[21] (17.5 g, 100 mmol), glycine (15.1 g, 200 mmol) and glacial acetic acid (50 mL) was refluxed for 3 h. After cooling to rt the reaction mixture was poured into ice water and the white crystals were filtered off and recrystallized from water to give **7** (15.6 g, 67%) mp 260-263°C. *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C,65.91; H, 5.15; N 12.18.

Table 9. Crystal data and structure refinement for **6f**.

Brutto formula	$C_{20}H_{19}N_3O_2$
Molecular weight	333.38
Temperature	293 (2) K
Wavelength	1.54178Å
Crystal system	Monoclinic
Space group	P $2_1/n$
Unit cell dimensions	a =10.074 (2) Å, α = 90 deg. b = 14.447 (2) Å, β = 99.65 (2) deg. c = 11.701 (3) Å, γ = 90 deg.
Volume	1678.7 (6) $Å^3$
Z	4
Density (calculated)	1.319 mg/m^3
Absorption coefficient	0.700 mm^{-1}
F(000)	704
Crystal size	0.7 x 0.6 x 0.2 mm
Theta range for data collection	4.91 to 75.15 deg.
Index ranges	-12 <=h<=12, -11 <=k<18, -14 <=l<=14
Reflections collected	3538
Independent reflections	3341 [R(int = 0.0750)]
Absorption correction	Semi-empirical from psi-scans
Max. and min. transmission	0.999 and 0.805
Refinement method	Full-matrix least-squares on F^2
Data / restrains / parameters	3339 / 0 /231
Goodness-of-fit on F^2	1.028
Final R indices [I > 2 sigma(I)]	R_1 =0.0685, wR_2 = 0.2034
R indices (all data)	R_1 =0.1161, wR_2 = 0.2584
Extinction coefficient	0.0051 (11)
Largest diff. peak and hole	0.247 and -0.281 e.$Å^3$

2-[2-(1-Bromoethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetic acid (8). To a solution of compound (7) (2.32 g, 10 mmol), NaOAc (0.82 mg, 10 mmol) and glacial acetic acid (15 mL) bromine (1.60 g, 10 mmol) in glacial acetic acid (5 mL) was added dropwise at 40-50 °C and the reaction mixture was stirred for 3 h. The reaction mixture was left to stand in a refrigerator overnight. The crystals were filtered off,

washed with water and recrystallized from 2-propanol to give compound (**8**) (2.27 g, 73%) mp 196-197°C. *Anal.* Calcd for $C_{12}H_{11}N_2O_3Br$: C, 46.32; H, 3.56; N, 9.00. Found: C,46.21; H,3.35; N 9.18.

1-Methyl-3,4-dihydro-1*H*,7*H*-[1,4]oxazino[3,4-*b*]quinazoline-3,6-dione (9). A solution of **8** (3.11 g, 10 mmol), triethylamine (2.02 g, 20 mmol) and $CHCl_3$ (20 mL) was stirred at rt for 3 h. The reaction mixture was extracted with 5 % AcOH (3x5 mL), then with water (3x5 mL). The dried organic phase was evaporated in vacuo to dryness and the residue was recrystallized from ethanol to give tricyclic compound (**9**) (1.73 g, 75%) mp 199-201°C. *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.71; H, 4.25; N, 12.18.

Table 10. Elementary Analyses for Compounds (**2**) and (**3**).

Compd No	Calcd C	H	N	Found C	H	N	Compd No	Calcd C	H	N	Found C	H	N
2a	63.48	5.86	22.21	63.53	5.99	22.34	**3d**	58.54	5.89	13.65	58.65	6.06	13.72
2b	65.01	6.45	20.67	64.79	6.61	20.68	**3e**	59.72	6.26	13.06	59.87	6.31	12.99
2c	66.34	6.96	19.34	66.43	6.99	19.28	**3f**	64.14	5.10	11.81	64.07	4.89	11.88
2d	67.51	7.41	18.17	67.68	7.55	18.10	**3h**	63.25	4.72	12.29	63.12	4.80	12.19
2e	68.54	7.81	17.13	68.72	7.79	17.24	**3i**	61.38	4.88	11.30	61.20	5.07	11.29
2f	73.10	6.13	15.04	73.26	5.98	15.11	**3j**	64.14	5.10	11.81	64.14	5.02	11.75
2g	73.70	6.53	14.32	73.78	6.64	14.44	**3k**	60.09	4.20	11.68	60.23	4.19	11.73
2h	72.43	5.70	15.84	72.60	5.67	15.80	**3l**	57.46	4.02	11.17	57.58	3.93	11.03
2i	69.14	5.80	14.23	69.22	5.87	14.31	**3m**	62.26	5.22	10.89	62.40	5.27	11.10
2j	73.10	6.13	15.04	72.89	6.11	15.09	**3p**	62.58	4.73	10.59	62.73	4.68	10.55
2k	67.83	4.98	14.83	68.04	5.00	14.84	**4b**	49.72	4.77	12.42	49.91	4.81	12.34
2l	64.11	4.71	14.02	64.23	4.77	14.00	**4c**	51.15	5.15	11.93	51.03	14.96	12.08
2m	69.88	6.19	13.58	70.09	6.12	13.67	**4d**	52.47	5.50	11.47	52.71	5.39	11.63
2n	70.33	4.86	19.30	70.35	4.97	19.27	**4e**	53.69	5.83	11.05	53.58	5.94	11.84
2o	61.26	4.23	12.61	61.34	4.21	12.69	**4f**	57.98	4.87	10.14	57.87	4.87	10.23
2p	70.34	5.58	13.67	70.48	5.65	13.81	**4h**	57.01	4.53	10.50	56.86	4.60	10.38
2q	61.93	4.55	18.05	62.12	4.43	17.95	**4i**	55.83	4.68	9.77	55.94	4.67	9.89
3a	54.25	4.55	15.81	54.43	4.64	15.87	**4k**	54.56	4.10	10.05	54.64	4.03	9.87
3b	55.82	5.04	15.02	55.68	4.88	15.14	**4m**	56.77	4.99	9.46	56.93	5.14	9.48
3c	57.24	5.49	14.30	57.42	5.53	14.41	**4p**	57.03	4.56	10.85	56.94	4.63	10.88

2-[2-(1-Hydroxyethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetanilide (10). A solution of **9** (3.21 g, 10 mmol) aniline (2.46 g, 25 mmol) in ethanol (30 mL) was heated under reflux for 3 h. The reaction mixture was evaporated in vacuo to dryness and residue was treated with 5% HCl solution (5 mL) and it was extracted with $CHCl_3$ (3x5 mL). The combined and dried organic phase was evaporated in vacuo to dryness and the residue was recrystallized from a mixture of 2-propanol and ether to give compound (**10**) (2.62 g, 81%) mp 181-184°C. *Anal.* Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.91; H, 5.15; N, 13.18.

Ethyl 3-[2-Ethyl-4-oxo-3,4-dihydroquinazolin-3-yl]acetate (11):

Method F: A solution of compound (**7**) (2.32 g, 10 mmol) in ethanol (20 mL) was saturated with dry HCl and heated under reflux for 5 h. The reaction mixture was evaporated in vacuo to dryness, and residue was dissolved in ether (50 mL). The organic phase was washed with saturated Na_2CO_3 solution (3x15 mL) and water (2x10 mL). The combined and dried organic phase was evaporated in vacuo to dryness. The residue was recrystallized from ether to give **11** (2.21 g, 85%) mp 191-193°C. *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.78; H, 6.14; N, 10.87.

Method G: 2-Ethylquinazolin-4(3*H*)-one[22] (17.4 g, 100 mmol) and ethyl chloroacetate (12.2 g, 100 mmol) were heated in ethanol (100 mL) in presence of NaOEt (6.8 g, 100 mmol) for 5 h. The reaction mixture was evaporated in vacuo to dryness, and residue was dissolved in ether (50 mL). The organic phase was washed with saturated Na_2CO_3 solution (3x15 mL) and water (2x10 mL). The combined and dried organic phase was evaporated in vacuo to dryness. The residue was recrystallized from ether to give **11** (1.74 g, 67%) mp 191-193°C.

Ethyl 3-[2-(1-Bromoethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetate (12). To a solution of compound (**11**) (2.60 g, 10 mmol), NaOAc (0.98 g, 12 mmol) and glacial acetic acid (20 mL) bromine (1.60 g, 10 mmol) in glacial acetic acid (5 mL) was added dropwise at and the reaction mixture was stirred at ambient temperature for 3 h. The reaction mixture was left to stand in a refrigerator overnight and the precipitated crystals were filtered off, washed with water. The dried crystals were recrystallized from ethanol to give **12** (2.81 g, 83%) mp 166-169°C. *Anal.* Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.58; H, 4.46; N, 8.26. Found: C, 49.70; H, 4.29; N, 8.19.

Ethyl 2-{2-[1-(Phenylamino)ethyl]-4-oxo-3,4-dihydroquinazolin-3-yl}acetate (13). A solution of compound (**12**) (3.41 g, 10 mmol) and aniline (1.86 g, 20 mmol) in ethanol (30 mL) was heated under reflux for 6 h, then the reaction mixture was evaporated in vacuo to dryness. The residue was dissolved in $CHCl_3$ (40 mL) and the solution was washed with saturated Na_2CO_3 (3x15 mL). The dried organic phase was evaporated in vacuo to dryness. The residue was recrystallized from 2-propanol to give compound (**13**) (3.02 g, 86%) mp. 172-174°C. *Anal.* Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.52; H, 6.11; N, 12.16.

1-Methyl-2-phenyl-1,2,3,4-tetrahydro-6*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (5h). Ethyl 2-{2-[1-(phenylamino)ethyl]-4-oxo-3,4-dihydroquinazolin-3-yl}acetate (**13**) (3.51 g, 10 mmol) was dissolved in toluene (30 mL) and was heated at 110 °C for 8 h. After cooling the mixture was washed with 5 % HCl (2x10 mL) and water (2x15 mL). The dried organic phase was evaporated in vacuo to dryness. The residue was recrystallized from ethanol to give compound (**5h**) (2.65 g, 78%) mp. 217-218°C.

REFERENCES

1. NBC 89: K. Simon, L. Pusztay, M. Hanusz, Zs. Böcskei, B. Podányi, M. Fehér, and I. Hermecz, *Heterocycles*, 1997, **45**, 2175.

2. S. Sinha and M. Srivastava, *Progress in Drug Research*, 1994, **43**, 143.

3. M. A. E. Sharan, M. A. M. Tama, and E. M. Sharshira, *Adv. Heterocycl. Chem.*, 1991, **52**, 97.

4. L. Vasvári-Debreczy, I. Hermecz, and P. Mátyus, *Compr. Heterocycl. Chem. II*, 1996, **8**, 633.

5. R. G. Griot, US 3,280,117 (*Chem. Abstr.*, 1967, **66**, 2584).

6. F. Pinnen, A. Di Muro, G. Zanotti, and G. Lucente, *Int. J. Peptide Protein Res.*, 1987, **30**, 388.

7. C. J. Barrow and H. H. Sun, *J. Nat. Product*, 1994, **57**, 471.

8. A. Numata, C. Takahashi, T. Matsushita, T. Miyamoto, K. Kawai, Y. Usami, E. Matsumura, M. Inoue, H. Ohishi, and T. Shingu, *Tetrahedron Lett.*, 1992, **33**, 1621.

9. C. Takahashi, T. Matsushita, M. Doi, K. Minoura, T. Shingu, Y. Kumeda, and A. Numata, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2345.

10. M. Otsuka and S. Konishi, *Trends NeuroSci. (Pers. Ed.)*, 1983, **6**, 317.

11. S. K. Kadam, P. E. Humphrey, J. Hochlowski, J. B. McAlpine, and M. Jackson, US 5,284,947 (*Chem. Abstr.*, 1994, **121**, 7435).

12. O. Meth-Cohn, H. Suschitzky, and M. E. Sutton, *J Chem. Soc., C*, 1968, 722.

13. B. Liberek and J. Zarebski, *Pept. Proc. Eur. Pept. Symp. 16th*, 1980, 236 (Pub. 1981) (*Chem. Abstr.*, 1982, **97**, 216690).

14. K. Hirai, T. Ishiba, H. Sugimoto, and T. Fujishima, *J. Org. Chem.*, 1981, **46**, 4489.

15. O. P. Rudenko, M. M. Botoshanskii, Y. A. Simonov, A. V. Bogatskii, and O. P. Povolotskaya, *Khim. Geterotsikl. Soedin.*, 1984, 983 (*Chem. Abstr.*, 1985, **102**, 6410).

16. F. He and B. B. Snider, *Synlett*, 1997, 483.

17. S. Rajappa and B. G. Advani, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2122.

18. S. Martin-Santamaria, F. L. Buenadícha, M. Espada, M. Söllhuber, and C. Avendaño, *J. Org. Chem.*, 1997, **62**, 6424.

19. P. S. N. Reddy and Ch. Nagaraju, *Synth. Commun.*, 1991, **21**, 173.

20. J. Kökösi, L. Örfi, M. Szabó, K. Takács-Novák, and Gy. Szász, *Magy. Kém. Folyóirat* 1991, **97**, 185 (*Chem. Abstr.* 1991, **115**, 159501).

21. D. T. Zentmyer, and E. C. Wagner, *J. Org. Chem.* 1949, **14**, 967.

22. R. S. Atkinson, and B. J. Kelly, *J. Chem. Soc., Perkin Trans.1*, 1989, 1657.

23. K. Suguna, S. Ramakumar, and S. Rajappa, *Acta Cryst.*, 1982, B**32**, 1654.

24. F. Johnson, *Chem. Rev.*, 1968, **68**, 375.

25. K. Nagarajan, R. K. Shah, H. Fuhrer, R. T. Puckett, M. R. Narasimhamurthy, and Venkatesan, K. *Helv. Chim. Acta*, 1978, **61**, 1246.

26. G. Tóth, I. Hermecz, and Z. Mészáros, *J. Heterocycl. Chem.*, 1979, **16**, 1181.

27. B. Podányi, I. Hermecz, L. Vasvári-Debreczy, and Á. Horváth, *J. Org. Chem.*, 1986, **51**, 394.

28. I. Hermecz, B. Podányi, Z. Mészáros, J. Kökösi, Gy. Szász, and G. Tóth, *J. Heterocycl. Chem.*, 1983, **20**, 93.

29. Atomic coordinates and further crystallographic details have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

30. J. C. A. Boeyens, *J. Cryst. Mol. Struct.*, 1978, **8**, 317.

Received, 11th May, 1998