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THE PICTET-SPENGLER REACTION IN THE SYNTHESIS OF CONDENSED BENZODIAZEPINES 1. SYNTHESIS OF 6,11,12,14-TETRAHYDROBENZO-[4,5][1,2]DIAZEPINO[7,1-*b*]QUINAZOLIN-14-ONES

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A new strategy is proposed for the synthesis of the seven-membered heterocyclic skeleton of tetrahydro[4,5][1,2]diazepino[7,1-b]quinazolin-14-ones based on the Pictet-Spengler reaction of 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one with aromatic aldehydes and paraform in acid media.

Keywords: 3-amino-2-(1,4-benzodioxan-6-ylmethyl)quinazolin-4(3H)-one, 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one, condensed diazepines, hydrochloric acid, tetrahydrobenzo[4,5][1,2]diazepino-[7,1-*b*]quinazolin-14-ones, trifluoroacetic acid, the Pictet-Spengler reaction, cyclization.

Condensed diazepine systems play an important role in pharmaceutical chemistry. The biological activity of diazepines, especially benzocondensed derivatives, is connected to their influence on the central nervous system. 2,3-Benzodiazepines, which are isomeric analogs to the 1,5- and 1,4-benzodiazepines, are of practical interest as potential medical preparations used for the treatment of neurodegenerative diseases of the CNS [1].

In distinction to 1,5- and 1,4-benzodiazepines, 2,3-benzodiazepines do not interact with benzodiazepine receptors, but are allosteric modulators and nonspecific antagonists of AMPA, subsites of the glutamate receptor [2], widely distributed in the nervous systems of animals and man. The modulators of AMPA receptors show, as a rule, "pure" anxiolytic and antidepressant effects, they improve learning and memory, and they possess nootropic and neuroprotective properties. The structure of 2,3-benzodiazepine was first reported in the tranquilizer Grandaxin [1]. At present there is second phase testing of the preparation Talampanel, which has prospective medical properties for the treatment of Parkinson's and Alzheimer's diseases and is effective for traumatic swelling of the human brain and also for inhibition of growth of tumors of the brain [3].

The wide use of benzodiazepines is checked by the small number fof methods or preparing them and the difficulty of obtaining the required starting materials for their synthesis. The basic method for their preparation is based on the cyclization of 1,5-dicarbonyl compounds or 2-benzopyrylium salts with hydrazine [4, 6]. Tetrahydrobenzodiazepines were obtained by reduction of the corresponding benzodiazepines [7].

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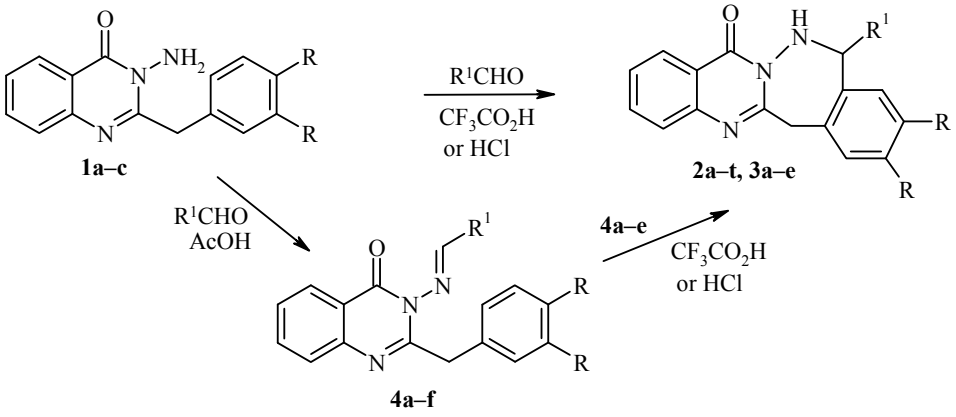
We have proposed a new strategy for the synthesis of the seven-membered heterocyclic skeleton of tetrahydrobenzo[4,5][1,2]diazepino[7,1-*b*]quinazolin-14-ones **2** and **3**, based on the interactions of 3-amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one (**1a**) and 3-amino-2-(1,4-benzodioxan-6-ylmethyl)quinazolin-4(3H)-one (**1b**) with aromatic aldehydes or paraform in acid media in the conditions of the Pictet-Spengler reaction.



1a–c **2a–t, 3a–e** **4a–f**

1 a R = OMe, **b** R = OCH_2CH_2O, **c** R = H; **2a–s** R = OMe, **a** R^1 = H, **b** R^1 = Ph, **c** R^1 = 4-MeC_6H_4, **d** R^1 = 2-MeC_6H_4, **e** R^1 = 4-HOC_6H_4, **f** R^1 = 3-$MeOC_6H_4$, **g** R^1 = 4-$MeOC_6H_4$, **h** R^1 = 3-MeO-4-HOC_6H_3, **i** R^1 = 3-HO-4-$MeOC_6H_3$, **j** R^1 = 3,4-$(MeO)_2C_6H_3$, **k** R^1 = 4-FC_6H_4, **l** R^1 = 3-ClC_6H_4, **m** R^1 = 4-ClC_6H_4, **n** R^1 = 3-BrC_6H_4, **o** R^1 = 4-$Me_2NC_6H_4$, **p** R^1 = 4-$O_2NC_6H_4$, **q** R^1 = 2,3-$Cl_2C_6H_3$, **r** R^1 = 2,6-$Cl_2C_6H_3$, **s** R^1 = 2,4-$Cl_2C_6H_3$; **t** R = R^1 = H; **3a–e** R = OCH_2CH_2O, **a** R^1 = H, **b** R^1 = 4-MeC_6H_4, **c** R^1 = 3-HOC_6H_4, **d** R^1 = 4-ClC_6H_4, **e** R^1 = 4-$MeSC_6H_4$; **4a–e** R = MeO, **a** R^1 = 4-MeC_6H_4, **b** R^1 = 4-FC_6H_4, **c** R^1 = 4-ClC_6H_4, **d** R^1 = 4-$O_2NC_6H_4$, **e** R^1 = 3-MeO-4-HOC_6H_3, **f** R = H, R^1 = 4-ClC_6H_4

Assuming that the reaction proceeds *via* the intermediate formation of the Schiff's bases **4a-e**, we synthesized some of these by boiling compound **1a** with aldehydes in acetic acid. The azomethynes obtained **4a-e** when heated in hydrochloric or trifluoroacetic acids cyclized to the corresponding diazepines **2c**,**h**,**k**,**m**,**p**. The determining factor for the formation of diazepines from the amino derivatives **1a**,**b** and the corresponding Schiff's bases **4a-e** is the presence in the benzyl unit of the 3-aminoquinazol-4-ones of donor substituents with a conformed orientation. In the absence of the donor substituent cyclization occurs only with formaldehyde with a 75% yield of the diazepine **2t.** Aromatic aldehydes, for example 4-chlorobenzaldehyde, only form the Schiff's base **4f** with 3-amino-2-benzylquinazolin-4(3H)-one (**1c**) even on prolonged heating (30 h). A peculiarity of the ^{1}H NMR spectra of the benzodiazepines **2a-t** and **3a-e** is the characteristic doublet of the protons of the CH_2 group of the diazepine ring in the 3.90-5.10 ppm region with J = 13-14 Hz, which indicates that the diazepin ring is not planar.

The use of hydrochloric acid as the cyclizing agent has a number of advantages over trifluoroacetic acid. As a rule the reaction with aromatic aldehydes is finished in 1-3 h and with a paraform in 10-20 min, whereas with trifluoroacetic acid it is necessary to heat for not less than 7 h which leads to side products connected with condensation of the diazepine with the initial aldehyde at the CH_2 group of the 2,3-benzodiazepine and also oxidation of the diazepines to dehydro derivatives. For example, on reaction of the aminoquinazoline **1a** with 4-methylbenzaldehyde in trifluoroacetic acid the diazepine **2c** was isolated in 65% yield. After crystallization of the diazepine **2c** and evaporation of the mother liquor, the following compounds were observed by ^{1}H NMR spectroscopy and chromato-mass spectroscopy:

1) diazepine **2c**, 27% of the mixture (414 $[M+1]^+$);

2) the styryl derivative **5** (not isolated pure), 42% of the mixture (516 $[M+1]^+$);

3) product of the oxidation of the styryl derivative **6**, 30% of the mixture (514 $[M+1]^+$).

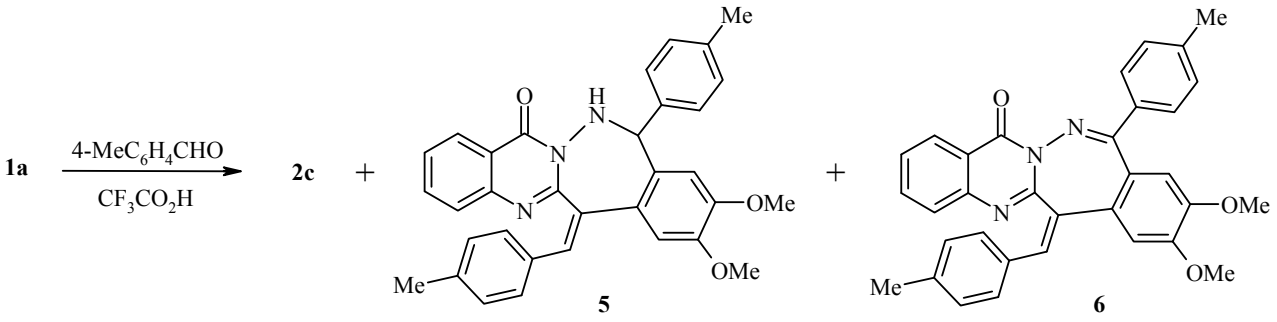
TABLE 1. Characteristics of the Compounds Synthesized, **1-4**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	Hal	N		
1	2	3	4	5	6	7	8
1a	$C_{17}H_{17}N_3O_3$	65.44 / 65.58	5.42 / 5.50	—	13.39 / 13.50	169	74
1b	$C_{17}H_{15}N_3O_3$	65.88 / 66.01	4.81 / 4.89	—	13.67 / 13.58	144	85
1c	$C_{15}H_{13}N_3O$	71.58 / 71.70	5.12 / 5.21	—	16.84 / 16.72	118-119	85
2A	$C_{18}H_{17}N_3O_3$	66.65 / 66.86	5.17 / 5.30	—	12.88 / 13.00	216-217	80 (A); 86 (B)
2b	$C_{24}H_{21}N_3O_3$	72.29 / 72.17	5.06 / 5.30	—	10.53 / 10.52	169	85 (B)
2c	$C_{25}H_{23}N_3O_3$	72.46 / 72.62	5.42 / 5.61	—	10.21 / 10.16	181-182 (with dec)	57 (A); 95 (B)
2d	$C_{25}H_{23}N_3O_3$	72.53 / 72.62	5.48 / 5.61	—	10.25 / 10.16	237-238 (with dec)	65 (A)
2e	$C_{24}H_{21}N_3O_4$	69.25 / 69.39	5.03 / 5.10	—	10.16 / 10.11	with dec >280	50 (A)
2f	$C_{25}H_{23}N_3O_4$	69.99 / 69.92	5.61 / 5.40	—	9.82 / 9.78	135-136	52 (A)
2g	$C_{25}H_{23}N_3O_4$	69.84 / 69.92	5.37 / 5.40	—	9.80 / 9.78	180-182	67 (A)
2h	$C_{25}H_{23}N_3O_5$	67.58 / 67.41	5.01 / 5.20	—	9.51 / 9.43	240	71 (B)
2i	$C_{25}H_{23}N_3O_5$	67.53 / 67.41	5.36 / 5.20	—	9.48 / 9.43	181-182	78 (B)
2j	$C_{26}H_{25}N_3O_5$	67.86 / 67.96	5.54 / 5.48	—	9.18 / 9.14	198	45 (A)
2k	$C_{24}H_{20}FN_3O_3$	69.00 / 69.06	4.87 / 4.83	4.56 / 4.55	10.09 / 10.07	209	60 (B)
2l	$C_{24}H_{20}ClN_3O_3$	66.15 / 66.44	4.47 / 4.65	8.11 / 8.17	9.73 / 9.68	213	52 (A)
2m	$C_{24}H_{20}ClN_3O_3$	66.26 / 66.44	4.76 / 4.65	8.03 / 8.17	9.59 / 9.68	187-189	65 (A)
2n	$C_{24}H_{20}BrN_3O_3$	60.01 / 60.26	4.07 / 4.21	16.60 / 16.70	8.89 / 8.78	211-212	80 (A)
2o	$C_{26}H_{26}N_4O_3$	70.32 / 70.57	5.77 / 5.92	—	12.69 / 12.66	136	50 (A); 82 (B)
2p	$C_{24}H_{20}N_4O_5$	64.98 / 64.86	4.43 / 4.54	—	12.72 / 12.61	200	62 (B)
2q	$C_{24}H_{19}Cl_2N_3O_3$	61.64 / 61.55	3.99 / 4.09	15.20 / 15.14	9.09 / 8.97	235-238	61 (A)
2r	$C_{24}H_{19}Cl_2N_3O_3$	61.49 / 61.55	4.21 / 4.09	15.12 / 15.14	9.04 / 8.97	227	56 (A)
2s	$C_{24}H_{19}Cl_2N_3O_3$	61.72 / 61.55	4.17 / 4.09	15.04 / 15.14	8.86 / 8.97	203	58 (A)
2t	$C_{16}H_{13}N_3O$	72.87 / 72.99	4.87 / 4.98	—	16.01 / 15.96	219-221	75 (B)
3a	$C_{18}H_{15}N_3O_3$	67.45 / 67.28	4.49 / 4.71	—	13.26 / 13.08	with dec >215 °C	40 (A)
3b	$C_{25}H_{21}N_3O_3$	72.75 / 72.98	5.01 / 5.14	—	10.27 / 10.21	214	43 (A)
3c	$C_{24}H_{19}N_3O_4$	69.88 / 69.72	4.64 / 4.63	—	10.03 / 10.16	210	86 (B)
3d	$C_{24}H_{18}ClN_3O_3$	66.47 / 66.75	4.03 / 4.20	8.11 / 8.21	9.52 / 9.73	168	50 (A)
3e*	$C_{25}H_{21}N_3O_3S$	67.53 / 67.70	4.85 / 4.77	—	9.22 / 9.47	226-228	50 (B)
4a	$C_{25}H_{23}N_3O_3$	72.53 / 72.62	5.46 / 5.61	—	10.09 / 10.16	164	95
4b	$C_{24}H_{20}FN_3O_3$	69.15 / 69.06	4.94 / 4.83	4.53 / 4.55	10.10 / 10.07	160-161	94

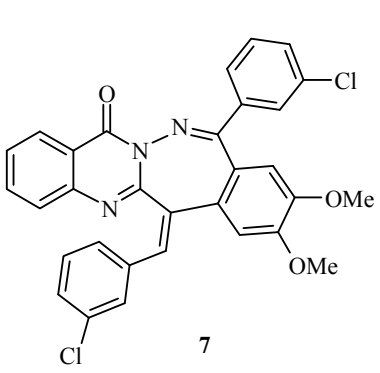
* Found, %: S 7.11. Calculated, %: S 7.23.

TABLE 1 (continued)

1	2	3	4	5	6	7	8
4c	$C_{24}H_{20}ClN_3O_3$	66.37 66.44	4.58 4.65	8.16 8.17	9.66 9.68	156-158	78
4d	$C_{24}H_{20}N_4O_5$	64.70 64.86	4.65 4.54	—	12.74 12.61	186	93
4e	$C_{25}H_{23}N_3O_5$	67.31 67.41	5.25 5.20	—	9.36 9.43	184-185	89
4f	$C_{22}H_{16}ClN_3O$	70.54 70.68	4.24 4.31	9.56 9.48	11.13 11.24	165	80
6	$C_{33}H_{27}N_3O_3$	77.28 77.17	5.35 5.30	—	8.23 8.18	213-214	7 (A); 50 (B)
7	$C_{31}H_{21}Cl_2N_3O_3$	67.04 67.16	3.98 3.82	12.74 12.79	7.62 7.58	235-238	5
8	$C_{31}H_{19}Cl_4N_3O_3$	59.70 59.74	3.15 3.07	22.69 22.75	6.80 6.74	262	6



8,9-Dimethoxy-11-(*p*-tolyl)-6-[(*p*-tolyl)methylidene]-6,14-dihydrobenzo[4,5][1,2]diazepino(7,1-*b*)quinazoline-14-one (**6**), like the analogous compounds **7** and **8**, was obtained by fractional crystallization of the residue after isolation of the diazepines **2c**,**l**,**s**.



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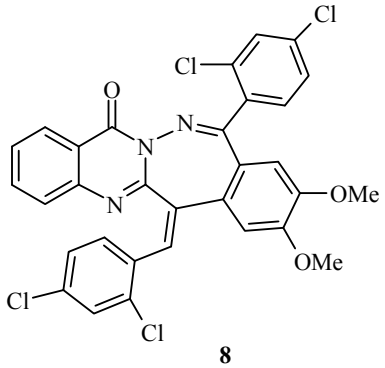

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The styryl derivatives **5** and **6** were formed in a control experiment by heating diazepine **2c** with 4-methylbenzaldehyde in trifluoroacetic acid (chromato-mass-spectroscopic data) with an overall yield of 10%. On heating a stoichiometric mixture of 4-methylbenzaldehyde with diazepine **2c** in DMF in the presence of potassium *tert*-butoxide at 60°C for 50 h [8], only compound **6** was isolated with a yield of 50%.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm. (*J*, Hz)
1	2
1a	3.76 and 3.78 (6H, s, 3'- and 4'-OCH_3); 4.26 (2H, s, CH_2); 5.50 (2H, s, NH_2); 6.80 (1H, d, *J* = 8.0, H-5'); 6.88 (1H, d, *J* = 8.0, H-6'); 6.98 (1H, s, H-2'); 7.43 (1H, t, *J* = 8.0, H-6); 7.61 (1H, d, *J* = 8.0, H-8); 7.72 (1H, t, *J* = 8.0, H-7); 8.12 (1H, d, *J* = 8.0, H-5)
1b	4.32 (2H, s, CH_2); 4.10-4.20 (4H, m, OCH_2CH_2O); 5.52 (2H, s, NH_2); 6.63 (1H, d, *J* = 8.0, H-6'); 6.74 (1H, s, H-2'); 6.75 (1H, d, *J* = 8.0, H-5'); 7.40 (1H, t, *J* = 8.0, H-6); 7.57 (1H, d, *J* = 8.0, H-8); 7.63 (1H, t, *J* = 8.0, H-7); 8.05 (1H, d, *J* = 8.0, H-5)
1c	4.32 (2H, s, CH_2); 5.52 (2H, s, NH_2); 7.16 (1H, t, *J* = 8.0, H-4'); 7.25 (2H, t, *J* = 8.0, H-3',5'); 7.35 (2H, d, *J* = 8.0, H-2',6'); 7.40 (1H, t, *J* = 8.0, H-6); 7.57 (1H, d, *J* = 8.0, H-8); 7.69 (1H, t, *J* = 8.0, H-7); 8.09 (1H, d, *J* = 8.0, H-5)
2a	3.70 and 3.80 (6H, s, 8- and 9-OCH_3); 4.34 (4H, br. s, 2- and 6-CH_2); 6.52 (1H, s, H-7); 6.76 (1H, s, H-10); 7.14 (1H, br. s, NH); 7.40 (1H, t, *J* = 8.0, H-2); 7.55 (1H, d, *J* = 8.0, H-4); 7.69 (1H, t, *J* = 8.0, H-3); 8.13 (1H, d, *J* = 8.0, H-1)
2b	3.57 and 3.86 (6H, s, 8- and 9-OCH_3); 3.90 and 5.15 (2H, d, *J* = 13.2, CH_2); 5.47 (1H, s, CH); 6.29 (1H, s, H-7); 6.48 (1H, d, *J* = 2.0, NH); 6.84 (1H, s, H-10); 7.35 (6H, m, H-2',3',4',5',6' and H-2); 7.59 (1H, d, *J* = 8.0, H-4); 7.81 (1H, t, *J* = 8.0, H-3); 8.12 (1H, d, *J* = 8.0, H-1)
2c	2.31 (3H, s, CH_3); 3.51 and 3.81 (6H, s, 8- and 9-OCH_3); 4.00 and 5.03 (2H, d, *J* = 14.2, CH_2); 5.48 (1H, s, CH); 6.29 (1H, s, H-7); 6.72 (1H, br. s, NH); 6.95 (1H, s, H-10); 7.12 (2H, d, *J* = 7.5, H-3',5'); 7.20 (2H, d, *J* = 7.5, H-2',6'); 7.47 (1H, t, *J* = 7.6, H-2); 7.61 (1H, d, *J* = 7.6, H-4); 7.77 (1H, t, *J* = 7.6, H-3); 8.05 (1H, d, *J* = 7.6, H-1)
2d	2.59 (3H, s, CH_3); 3.51 and 3.84 (6H, s, 8- and 9-OCH_3); 3.93 and 5.15 (2H, d, *J* = 12.8, CH_2); 5.66 (1H, s, CH); 6.17 (1H, s, H-7); 6.70 (1H, br. s, NH); 6.93 (1H, s, H-10); 7.00-7.08 (2H, m, H-3',5'); 7.20 (1H, t, *J* = 7.4, H-4'); 7.24 (1H, d, *J* = 7.4, H-6'); 7.46 (1H, t, *J* = 8.0, H-2); 7.61 (1H, d, *J* = 8.0, H-4); 7.75 (1H, t, *J* = 8.0, H-3); 8.09 (1H, d, *J* = 8.0, H-1)
2e	3.49 and 3.79 (6H, s, 8- and 9-OCH_3); 4.05 and 4.98 (2H, d, *J* = 13.6, CH_2); 5.44 (1H, s, CH); 6.32 (1H, s, H-7); 6.67 (2H, d, *J* = 7.6, H-3',5'); 6.70 (1H, br. s, NH); 6.97 (1H, s, H-10); 7.06 (2H, d, *J* = 7.6, H-2',6'); 7.47 (1H, t, *J* = 7.6, H-2); 7.61 (1H, d, *J* = 7.6, H-4); 7.78 (1H, t, *J* = 7.6, H-3); 8.03 (1H, d, *J* = 7.6, 1-H); 9.30 (1H, s, OH)
2f	3.55 and 3.83 (6H, s, 8- and 9-OCH_3); 3.73 (3H, s, 3'-OCH_3); 3.97 and 5.06 (2H, d, *J* = 13.6, CH_2); 5.44 (1H, s, CH); 6.29 (1H, s, H-7); 6.59 (1H, br. s, NH); 6.80-6.90 (4H, m, H-2',4',6',10); 7.21 (1H, t, *J* = 8.0, H-5'); 7.41 (1H, t, *J* = 8.0, H-2); 7.58 (1H, d, *J* = 8.0, H-4); 7.70 (1H, t, *J* = 8.0, H-3); 8.08 (1H, d, *J* = 8.0, H-1)
2g	3.55 and 3.83 (6H, s, 8- and 9-OCH_3); 3.70 (3H, s, 4'-OCH_3); 4.00 and 5.00 (2H, d, *J* = 14.3, CH_2); 5.50 (1H, s, CH); 6.24 (1H, s, H-7); 6.59 (1H, br. s, NH); 6.87 (1H, s, H-10); 7.30 (4H, m, H-2',6' and H-3',5'); 7.42 (1H, t, *J* = 7.6, H-2); 7.57 (1H, d, *J* = 7.6, H-4); 7.71 (1H, t, *J* = 7.6, H-3); 8.05 (1H, d, *J* = 7.6, H-1)
2h	3.58 and 3.85 (6H, s, 8- and 9-OCH_3); 3.74 (3H, s, 3'-OCH_3); 3.97 and 5.05 (2H, d, *J* = 13.2, CH_2); 5.35 (1H, s, CH); 6.33 (1H, s, H-7); 6.52 (1H, br. s, NH); 6.72-6.81 (3H, m, H-2',5',6'); 6.85 (1H, s, H-10); 7.43 (1H, t, *J* = 7.6, H-2); 7.59 (1H, d, *J* = 7.6, H-4); 7.72 (1H, t, *J* = 7.6, H-3); 8.10 (1H, d, *J* = 7.6, H-1); 8.43 (1H, s, OH)
2i	3.56 (3H, s, 4'-OCH_3); 3.82 and 3.84 (6H, s, 8- and 9-OCH_3); 3.86 and 5.15 (2H, d, *J* = 13.2, CH_2); 5.30 (1H, s, CH); 6.30 (1H, s, H-7); 6.41 (1H, br. s, NH); 6.73 (1H, d, *J* = 7.6, H-5'); 6.80 (1H, s, H-2'); 6.81 (1H, d, *J* = 7.6, H-6'); 6.85 (1H, s, H-10); 7.42 (1H, t, *J* = 7.6, H-2); 7.58 (1H, d, *J* = 7.6, H-4); 7.71 (1H, t, *J* = 7.6, H-3); 8.11 (1H, d, *J* = 7.6 , H-1); 8.45 (1H, s, OH)
2j	3.50 and 3.80 (6H, s, 8- and 9-OCH_3); 3.63 and 3.74 (6H, s, 3'- and 4'-OCH_3); 4.06 and 4.93 (2H, d, *J* = 13.3, CH_2); 5.43 (1H, s, CH); 6.33 (1H, s, H-7); 6.71 (1H, s, NH); 6.81 (3H, br. s, H-2',5',6'); 6.91 (1H, s, H-10); 7.43 (1H, t, *J* = 8.0, H-2); 7.58 (1H, d, *J* = 8.0, H-4); 7.73 (1H, t, *J* = 8.0, H-3); 8.04 (1H, d, *J* = 8.0, H-1)
2k	3.54 and 3.83 (6H, s, 8- and 9-OCH_3); 4.11 and 4.96 (2H, br. s, CH_2); 5.58 (1H, d, *J* = 2.1, CH); 6.29 (1H, s, H-7); 6.88 (1H, br. s, NH); 6.95 (1H, s, H-10); 7.06 (2H, br. m, H-2',6'); 7.34 (2H, br. m, H-3',5'); 7.64 (1H, t, *J* = 7.6, H-2); 7.61 (1H, d, *J* = 7.6, H-4); 7.76 (1H, t, *J* = 7.6, H-3); 8.05 (1H, d, *J* = 7.6, H-1)

TABLE 2 (continued)

1	2
2l	3.53 and 3.81 (6H, s, 8- and 9-OCH_3); 4.12 and 4.88 (2H, br. s, CH_2); 5.55 (1H, s, CH); 6.29 (1H, s, H-7); 6.92 (1H, s, H-10); 6.98 (1H, br. s, NH); 7.15-7.30 (4H, m, H-2',4',5',6'); 7.42 (1H, t, *J* = 7.6, H-2); 7.58 (1H, d, *J* = 7.6, H-4); 7.72 (1H, t, *J* = 7.6, H-3); 8.01 (1H, d, *J* = 7.6, H-1)
2m	3.51 and 3.80 (6H, s, 8- and 9-OCH_3); 4.20 and 4.82 (2H, d, *J* = 13.4, CH_2); 5.62 (1H, s, CH); 6.33 (1H, s, H-7); 7.00 (1H, s, H-10); 7.10 (1H, br. s, NH); 7.30 (4H, m, H-2',3',5',6'); 7.46 (1H, t, *J* = 7.6, H-2); 7.63 (1H, d, *J* = 7.6, H-4); 7.76 (1H, t, *J* = 7.6, H-3); 8.00 (1H, d, *J* = 7.6, H-1)
2n	3.55 and 3.87 (6H, s, 8- and 9-OCH_3); 4.10 and 4.80 (2H, br. s, CH_2); 5.50 (1H, s, CH); 6.30 (1H, s, H-7); 6.94 (1H, s, H-10); 6.90 (1H, br. s, NH); 7.15-7.30 (4H, m, H-2',4',5',6'); 7.42 (1H, t, *J* = 7.6, H-2); 7.58 (1H, d, *J* = 7.6, H-4); 7.72 (1H, t, *J* = 7.6, H-3); 8.01 (1H, d, *J* = 7.6, H-1)
2o	2.95 (6H, s, $N(CH_3)_2$); 3.53 and 3.83 (6H, s, 8- and 9-OCH_3); 3.83 and 5.18 (2H, br. d, CH_2); 5.28 (1H, br. s, CH); 6.23 (1H, s, H-7); 6.31 (1H, br. s, NH); 6.64 (2H, d, *J* = 8.2, H-3',5'); 6.80 (1H, s, H-10); 7.16 (2H, d, *J* = 8.2, H-2',6'); 7.41 (1H, t, *J* = 7.6, H-2); 7.57 (1H, d, *J* = 7.6, H-4); 7.69 (1H, t, *J* = 7.6, H-3); 8.10 (1H, d, *J* = 7.6, H-1)
2p	3.54 and 3.82 (6H, s, 8- and 9-OCH_3); 4.21 and 4.84 (2H, d, *J* = 13.2, CH_2); 5.74 (1H, s, CH); 6.30 (1H, s, H-7); 6.94 (1H, s, H-10); 7.11 (1H, br. s, NH); 7.41 (1H, t, *J* = 8.0, H-2); 7.53 (2H, d, *J* = 8.0, H-2',6'); 7.59 (1H, d, *J* = 8.0, H-4); 7.73 (1H, t, *J* = 8.0, H-3); 7.99 (1H, d, *J* = 8.0, H-1); 8.09 (2H, d, *J* = 8.0, H-3',5')
2q	3.56 and 3.84 (6H, s, 8- and 9-OCH_3); 4.30 and 4.71 (2H, d, *J* = 13.0, CH_2); 6.10 (1H, s, CH); 6.30 (1H, s, H-7); 6.75 (1H, br. s, NH); 6.95 (1H, s, H-10); 7.01 (2H, m, H-4',6'); 7.43 (2H, m, H-2,5'); 7.58 (1H, d, *J* = 8.0, H-4); 7.72 (1H, t, *J* = 8.0, H-3); 7.98 (1H, d, *J* = 8.0, H-1)
2r	3.56 and 3.84 (6H, s, 8- and 9-OCH_3); 3.91 and 5.21 (2H, d, *J* = 13.2, CH_2); 6.14 (1H, s, H-7); 6.24 (1H, s, CH); 6.67 (1H, br. s, NH); 6.84 (1H, s, H-10); 7.32 (2H, m, H-4',5'); 7.42 (1H, t, *J* = 8.0, H-2); 7.54 (1H, d, *J* = 8.0, H-3'); 7.60 (1H, d, *J* = 8.0, H-4); 7.71 (1H, t, *J* = 8.0, H-3); 8.14 (1H, d, *J* = 8.0, H-1)
2s	3.59 and 3.86 (6H, s, 8- and 9-OCH_3); 4.22 and 4.78 (2H, d, *J* = 12.4, CH_2); 6.00 (1H, s, CH); 6.26 (1H, s, H-7); 6.87 (2H, br. s, NH, H-6'); 6.90 (1H, s, H-10); 7.06 (1H, d, *J* = 8.0, H-5'); 7.40 (1H, t, *J* = 8.0, H-2); 7.50 (1H, s, H-3'); 7.58 (1H, d, *J* = 8.0, H-4); 7.70 (1H, t, *J* = 8.0, H-3); 8.02 (1H, d, *J* = 8.0, H-1)
2t	4.41 (2H, s, 6-CH_2); 4.45 (2H, s, 11-CH_2); 7.05 (1H, d, *J* = 7.2, H-7); 7.17 (2H, m, H-8,9); 7.28 (1H, d, *J* = 7.2, H-10); 7.33 (1H, s, NH; 7.46 (1H, t, *J* = 8.0, H-2); 7.58 (1H, d, *J* = 8.0, H-4); 7.74 (1H, t, *J* = 8.0, H-3); 8.12 (1H, d, *J* = 8.0, H-1)
3a	4.18 (8H, m, 6- and 15-CH_2, OCH_2CH_2O); 6.45 (1H, s, H-16); 6.72 (1H, s, H-5); 7.12 (1H, s, NH); 7.42 (1H, t, *J* = 7.6, H-11); 7.55 (1H, d, *J* = 7.6, H-13); 7.69 (1H, t, *J* = 7.6, H-12); 8.12 (1H, d, *J* = 7.6, H-10)
3b	2.33 (3H, s, CH_3); 3.83 and 5.06 (2H, d, *J* = 13.2, CH_2); 4.13 (4H, m, OCH_2CH_2O); 5.33 (1H, s, CH); 6.19 (1H, s, H-16); 6.55 (1H, s, NH); 6.79 (1H, s, H-5); 7.11 (2H, d, *J* = 8.0, H-3',5'); 7.21 (2H, d, *J* = 8.0, H-2',6'); 7.43 (1H, t, *J* = 8.0, H-11); 7.57 (1H, d, *J* = 8.0, H-13); 7.72 (1H, t, *J* = 8.0, H-12); 8.06 (1H, d, *J* = 8.0, H-10)
3c	3.80 and 5.14 (2H, d, *J* = 13.2, CH_2); 4.16 (4H, m, OCH_2CH_2O); 5.28 (1H, s, CH); 6.29 (1H, s, H-16); 6.48 (1H, br. s, NH); 6.72 (1H, d, *J* = 7.6, H-4'); 6.77 (1H, d, *J* = 7.6, H-6'); 6.80 (2H, s, H-5,2'); 7.12 (1H, t, *J* = 7.6, H-5'); 7.43 (1H, t, *J* = 8.0, H-11); 7.59 (1H, d, *J* = 8.0, H-13); 7.72 (1H, t, *J* = 8.0, H-12); 8.12 (1H, d, *J* = 8.0, H-10); 9.06 (1H, s, OH)
3d	3.95 and 4.95 (2H, d, *J* = 13.2, CH_2); 4.11 (4H, m, OCH_2CH_2O); 5.43 (1H, s, CH); 6.20 (1H, s, H-16); 6.72 (1H, br. s, NH); 6.81 (1H, s, H-5); 7.36 (4H, m, H-2',3',5',6'); 7.43 (1H, t, *J* = 8.0, H-11); 7.55 (1H, d, *J* = 8.0, H-13); 7.69 (1H, t, *J* = 8.0, H-12); 8.04 (1H, d, *J* = 8.0, H-10)
3e	2.45 (3H, s, SCH_3); 3.88 and 5.01 (2H, d, *J* = 13.2, CH_2); 4.13 (4H, m, OCH_2CH_2O); 5.38 (1H, s, CH); 6.23 (1H, s, H-16); 6.61 (1H, br. s, NH); 6.81 (1H, s, H-5); 7.18 (2H, d, *J* = 8.0, H-3',5'); 7.25 (2H, d, *J* = 8.0, H-2',6'); 7.43 (1H, t, *J* = 8.0, H-11); 7.58 (1H, d, *J* = 8.0, H-13); 7.72 (1H, t, *J* = 8.0, H-12); 8.06 (1H, d, *J* = 8.0, H-10)
4a	2.33 (3H, s, CH_3); 3.53 and 3.68 (6H, s, 3'- and 4'-OCH_3); 4.15 (2H, s, CH_2); 6.54 (1H, d, *J* = 8.0, H-6'); 6.69 (1H, s, H-2'); 6.70 (1H, d, *J* = 8.0, H-5'); 7.11 (2H, d, *J* = 8.0, H-3'',5''); 7.48 (1H, t, *J* = 8.0, H-6); 7.62 (1H, d, *J* = 8.0, H-8); 7.75 (1H, t, *J* = 8.0, H-7); 7.85 (2H, d, *J* = 8.0, H-2'',6''); 8.16 (1H, d, *J* = 8.0, H-5); 8.64 (1H, s, CH=N)

TABLE 2 (continued)

1	2
4b	3.50 and 3.69 (6H, s, 3- and 4-OCH_3); 4.17 (2H, s, CH_2); 6.63 (1H, d, *J* = 8.8, H-6'); 6.74 (1H, s, H-2'); 6.75 (1H, d, *J* = 8.8, H-5'); 7.27 (2H, t, *J* = 8.7, H-3",5"); 7.46 (1H, t, *J* = 6.8, H-6); 7.67 (1H, d, *J* = 6.8, H-8); 7.75 (1H, t, *J* = 6.8, H-7); 7.95 (2H, t, *J* = 8.7, H-2",6"); 8.18 (1H, d, *J* = 6.8, H-5); 8.72 (1H, s, CH=N)
4c	3.51 and 3.54 (6H, s, 3- and 4-OCH_3); 4.19 (2H, s, CH_2); 6.73 (1H, d, *J* = 8.0, H-6'); 6.78 (1H, d, *J* = 8.0, H-5'); 6.79 (1H, s, *J* = 8.0, H-2'); 7.22 (2H, d, *J* = 7.6, H-3",5"); 7.41 (1H, t, *J* = 7.6, H-6); 7.63 (1H, d, *J* = 7.6, H-8); 7.71 (1H, t, *J* = 7.6, H-7); 7.88 (2H, d, *J* = 7.6, H-2",6"); 8.17 (1H, d, *J* = 7.6, H-5); 8.76 (1H, s, CH=N)
4d	3.60 and 3.71 (6H, s, 3- and 4-OCH_3); 4.25 (2H, s, CH_2); 6.68 (1H, d, *J* = 8.0, H-6'); 6.77 (1H, d, *J* = 8.0, H-5'); 6.81 (1H, s, H-2'); 7.49 (1H, t, *J* = 8.0, H-6); 7.71 (1H, d, *J* = 8.0, H-8); 7.78 (1H, t, *J* = 8.0, H-7); 8.15 (2H, d, *J* = 8.8, H-2",6"); 8.21 (1H, d, *J* = 8.0, H-5); 8.35 (2H, d, *J* = 8.8, H-3",5"); 9.19 (1H, s, CH=N)
4e	3.48 and 3.70 (6H, s, 3- and 4-OCH_3); 3.92 (3H, s, 3'-OCH_3); 4.16 (2H, s, CH_2); 6.68 (1H, d, *J* = 8.0, H-6'); 6.75 (1H, s, H-2'); 6.78 (1H, d, *J* = 8.0, H-5'); 6.91 (1H, d, *J* = 8.0, H-5"); 7.22 (1H, d, *J* = 8.0, H-6"); 7.46 (2H, m, H-2",6); 7.68 (1H, d, *J* = 8.0, H-8); 7.76 (1H, t, *J* = 8.0, H-7); 8.16 (1H, d, *J* = 8.0, H-5); 8.38 (1H, s, CH=N); 9.69 (1H, s, OH)
4f	4.26 (2H, s, CH_2); 7.11-7.18 (3H, m, H-3',4',5'); 7.23 (2H, d, *J* = 8.2, H-2',6'); 7.47 (1H, t, *J* = 8.0, H-6); 7.51 (2H, d, *J* = 8.8, H-3",5"); 7.67 (1H, d, *J* = 8.0, H-8); 7.77 (1H, t, *J* = 8.0, H-7); 7.83 (2H, d, *J* = 8.8, H-2",6"); 8.16 (1H, d, *J* = 8.0, H-5); 8.78 (1H, s, CH=N)
6	2.20 (3H, s, 4-CH_3); 2.47 (3H, s, 4'-CH_3); 3.53 and 3.75 (6H, s, 3- and 4-OCH_3); 6.94 (1H, s, H-7); 7.00 (2H, d, *J* = 7.5, H-3',5'); 7.02 (1H, s, H-10); 7.17 (1H, s, CH=); 7.28 (1H, t, *J* = 7.6, H-2); 7.34 (4H, m, H-3",5" and H-2',6'); 7.67 (2H, m, H-3,4); 7.78 (2H, d, *J* = 7.5, H-2",6"); 8.33 (1H, d, *J* = 8.0, H-1)
7	3.58 and 3.79 (6H, s, 8- and 9-OCH_3); 6.93 (1H, s, H-7); 7.11 (1H, s, H-10); 7.20-7.38 (4H, m, H-4',5' [6- and 11-(3-Cl-Ph)]); 7.34 (1H, s, CH=); 7.59 (1H, t, *J* = 8.0, H-3); 7.62 (1H, d, *J* = 8.2, H-6' [6-(3-Cl-Ph)]); 7.66 (1H, s, H-2' [11-(3-Cl-Ph)]); 7.72 (1H, d, *J* = 8.0, H-4); 7.82 (1H, t, *J* = 8.0, H-2); 7.89 (1H, d, *J* = 8.2, H-6' [11-(3-Cl-Ph)]); 7.92 (1H, s, H-2' [6-(3-Cl-Ph)]); 8.37 (1H, d, *J* = 8.0, H-1)
8	3.50 and 3.73 (6H, s, 8- and 9-OCH_3); 6.34 (1H, s, H-7); 7.00 (1H, s, H-10); 7.20 (1H, d, *J* = 8.2, H-5' [6-(2,4-Cl_2-Ph)]); 7.35 (1H, t, *J* = 8.0, H-3); 7.37 (1H, d, *J* = 8.2, H-6' [6-(2,4-Cl_2-Ph)]); 7.45 (1H, s, CH=); 7.51 (1H, s, H-3' [11-(2,4-Cl_2-Ph)]); 7.52 (1H, d, *J* = 8.2, H-5' [11-(2,4-Cl_2-Ph)]); 7.34 (1H, d, *J* = 8.2, H-6' [11-(2,4-Cl_2-Ph)]); 7.62 (1H, d, *J* = 8.0, H-4); 7.75 (1H, s, H-3' [6-(2,4-Cl_2-Ph)]); 7.78 (1H, t, *J* = 8.0, H-2); 8.39 (1H, d, *J* = 8.0, H-1)

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal were recorded on Gemini-200 (200 MHz) and Bruker Avance II 400 (400 MHz) instruments, chromato-mass spectra were recorded on an Agilent 1100 LC/MSD VL spectrometer with chemical positive ionization at atmospheric pressure (APCI). Parameters of the chromatographic column: length 50 mm, diameter 4.6 mm, stationery phase ZORBAX SB-C18, solvent 95:5 acetonitrile–water, 0.1% trifluoroacetic acid, gradient elution, rate of flow of solvent 3.0 ml/min. Characteristics of the compounds synthesized are cited in Tables 1 and 2.

3-Amino-2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one (1a), 3-Amino-2-(1,4-benzodioxan-6-ylmethyl)- quinazolin-4(3H)-one (1b), and 3-Amino-2-benzylquinazolin-4(3H)-one (1c) were obtained by cyclization of methyl esters of 2-(3,4-dimethoxybenzylcarboxamido)-, 2-(1,4-benzodioxan-6-ylmethylcarboxamido)-, and 2-(benzylcarboxamido)benzoic acids with hydrazine hydrate by a method analogous to literature methods [9, 10].

3-Arylmethylideneamino-2-benzylquinazolin-4(3H)-ones (Schiff's Bases) 4a-f (General Method): A solution of the corresponding 3-amino-2-benzylquinazolin-4(3H)-one **1a-c** (2.5 mmol) and an aromatic aldehyde (2.5 mmol) in acetic acid (5 ml) was boiled for 5 h, cooled and diluted with water. The crystals which precipitated were filtered off and recrystallized from ethanol.

8,9-Dimethoxy-6,11,12,14-tetrahydrobenzo[4,5][1,2]diazepino[7,1-*b*]quinazolin-14-ones, 2a-t, 3a-e (General Method). A. A mixture of the corresponding amino derivative **1a**,**b** (2.5 mmol) and an aldehyde (2.5 mmol) in trifluoroacetic acid (4 ml) was boiled for 7-8 h. The reaction mixture was cooled, diluted with water and neutralized with 10% aqueous ammonia to a weakly alkaline reaction. The mixture was kept for 1 h, the crystals were filtered off and washed with water. They were recrystallized from acetone or a DMF–acetonitrile mixture. Compound **2o** was purified by recrystallization from 2-propanol or acetone.

B. A mixture of the corresponding amino derivative **1a**,**b** (2.5 mmol) and an aldehyde (2.5 mmol) in HCl (10 ml) was stirred for 2-3 h at 90°C. For better solution of the starting materials freshly distilled dioxane (1-3 ml) can be added. The reaction mixture was cooled and treated as in method A. Compounds **2a,c** and **3c** crystallized from the reaction mixture on cooling and can be isolated as their hydrochlorides. Conversion into the base can be effected with aqueous ammonia solution.

C. Cyclization of the Schiff's bases **4a-e** was carried out by boiling in trifluoroacetic acid for 7 h.

8,9-Dimethoxy-11-(*p*-tolyl)-6-[(*p*-tolyl)methylidene)-6,14-dihydrobenzo[4,5][1,2]diazepino[7,1-*b*]quinazolin-14-one (6). t-BuOK (0,34 g, 3 mmol) was added to a solution of compound **2c** (0.95 g, 2.3 mmol) in DMF (7 ml) and *p*-tolylaldehyde (0.55 g, 2.3 mmol) and the mixture was stirred for 50 h at 60°C. The mixture was cooled, diluted with water (20 ml) and neutralized with formic acid. The precipitate was filtered off and recrystallized from acetonitrile.

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