Synthesis and properties of 1,2-dihydro-4(3*H*)-quinazolinones

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We modified the preparative-scale method for the synthesis of 2-aryl 1,2-dihydro-4(3*H*)-quinazolinone derivatives obtained in high yields by the reaction of new and commercially available aromatic aldehydes with anthranilic acid amides. A series of quinazolinone derivatives possessing anticancer and antiparasitic activities, as well as capable of preventing the progress of neurodegenerative diseases were characterized. There are grounds for clinical trials of these substances in order to select compounds being promising for clinical application.

Key words: anthranilamides, aromatic aldehydes, quinazolinones, stereochemistry, cyclocondensation, inhibition of signaling pathways, blocking of DNA repair, anticancer drugs, neurodegenerative diseases.

One of the most promising strategies for the therapy of cancer, autoimmune, and some neurodegenerative diseases is the application of targeted drugs. The basis for targeted therapy is the presence of a target in the cell signaling pathway which can be affected using a substance possessing a high affinity to this target. If certain signaling pathway is active predominantly in a tumor cell or a cell responsible for autoimmunity, the interruption of this pathway can result in the death of such cell populations. Normal cells will remain unaffected.

To expand the range of already known targeted drugs, numerous new compounds are being synthesized and studied worldwide annually. Among them are quinazolinone and its derivatives. Quinazolinone derivatives are known to possess some significant pharmacological effects. Different researchers consider them as antibiotics,[1] cardiostimulators,[2] vasodilators,[3] and analgetics.[4] In addition, these derivatives extensively suppress the proliferation of tumor cells.[5] In Refs 6 and 7, the reduction of 4-quinazolinones with sodium borohydride afforded the 1,2-dihydro derivatives which possess a higher bioactivity than their precursors.

For this reason, the development of convenient preparation methods and the synthesis of a wide range of new 1,2-dihydro-4(3*H*)-quinazolinones seem to be a topical problem.

Among known available routes for the synthesis of structures to be sought (Scheme 1), the route *B* appears to be the most attractive, since, in our opinion, it allows one to obtain more various 4-quinazolinones by varying substituents in the used anthranilic acid amides and aldehydes.

The present work is dedicated to the study of both starting anthranilic acid amides and final 1,2-dihydro-4(3*H*)-quinazolinone derivatives and summarizes the results of our studies performed in recent years.

Results and Discussion

Synthesis of anthranilic acid derivatives

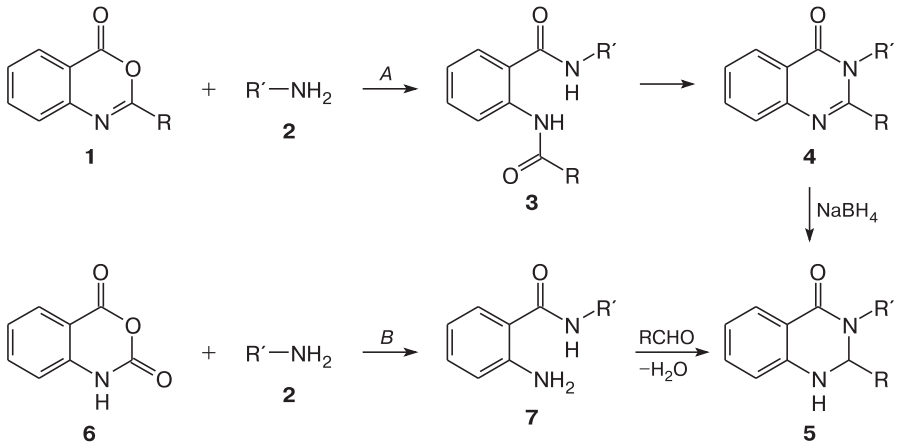
One of the most common methods for the synthesis of anthranilic acid amides **7** based on the reaction of isatoic anhydride **6** with aliphatic and aromatic amines[8—10] (see Scheme 1) was found to be unsuitable for our purposes due to side processes, which does not provide satisfactory yields of target compounds.[11] Therefore, we chose an alternative one-pot phosphaso method including the preparation step of phosphorylenimine amides **8** (Scheme 2).

When various amines are involved in the above-mentioned reaction, aliphatic and aromatic amines were found to smoothly react with anthranilic acid affording derivatives of anthranilic acid amide in high yields. For example, propyl-, phenyl-, and 4-substituted phenylamides, as well as furfuryl-, benzyl, and aminoalkylamides **7a—h** were obtained by this method in yields of 70—80%. The exception was 2,6-disubstituted phenylamines and tertiary alkylamines, the use of which resulted in oligomerization of anthranilic acid instead of amidation due to steric hindrances (the starting amines were regenerated).

The structures of synthesized compounds were determined from the comparison of their physicochemical

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1044—1058, June, 2017.

Scheme 1



R = Alk, Ar; R′ = Alk, Ar, Het

constants with known samples and some of these structures were additionally confirmed by the analysis of ^{1}H NMR spectra and data from elemental analysis (Table 1).

Thus, the chosen route allowed us to synthesize eight derivatives of anthranilic acid amides and to determine the range of applicability of this method.

Synthesis of anisaldehyde derivatives

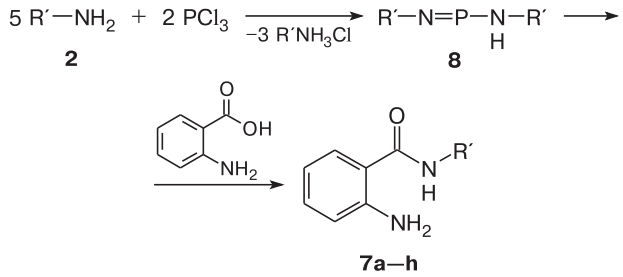
Chloromethylation used to introduce functional groups into the aromatic ring is known to proceed most smoothly in the case of aromatic substrates activated with electron-donating substituents. It is also known that the presence of methoxy substituents in the benzene ring favors an increase in the bioactivity. Therefore, we chose anisaldehyde as the research object and synthesized new aromatic aldehydes by its chloromethylation followed by substitution of different nucleophiles for the chlorine atom.

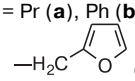
These studies allowed us to develop a method for the preparative-scale preparation of 4-methoxy-3-chloromethylbenzaldehyde by the reaction of which with different NH, OH, and SH acids about one hundred of new aromatic aldehydes have been synthesized (for details, see Refs 12 and 13).

Synthesis of 1,2-dihydro-4(3H)-quinazolinones

The literature data on the synthesis of quinazolinones[6,7,14] by the above-chosen route (see the preamble) include the reaction of anthranilic acid amides **7** with aliphatic or heteroaromatic aldehydes or their acetals in ethanol under the action of hydrochloric acid. Our attempts to use the synthesized aromatic aldehydes under these conditions does not lead to positive solutions (the starting reagents were isolated). Therefore, to find conditions for this process, we tested different commonly known methods by the example of reaction between the substituted anisaldehyde **9** and anthranilic acid benzylamide **7g**, which results in the intermediate formation of Schiff bases **10** (Scheme 3). However, all these attempts resulted in either compound **10** or a mixture of compounds **10** and **11m** most likely due to the fact that, under selected conditions, intermediates **10** are poorly soluble and, until completion of the process, precipitate either individually or as a mixture with the final quinazolinone **11m**.

Scheme 2



R′ = Pr (**a**), Ph (**b**), 4-MeOC$_6$H$_4$ (**c**), 4-FC$_6$H$_4$ (**d**), 4-MeC$_6$H$_4$ (**e**),  (**f**), Bn (**g**), $CH_2CH_2NEt_2$ (**h**)

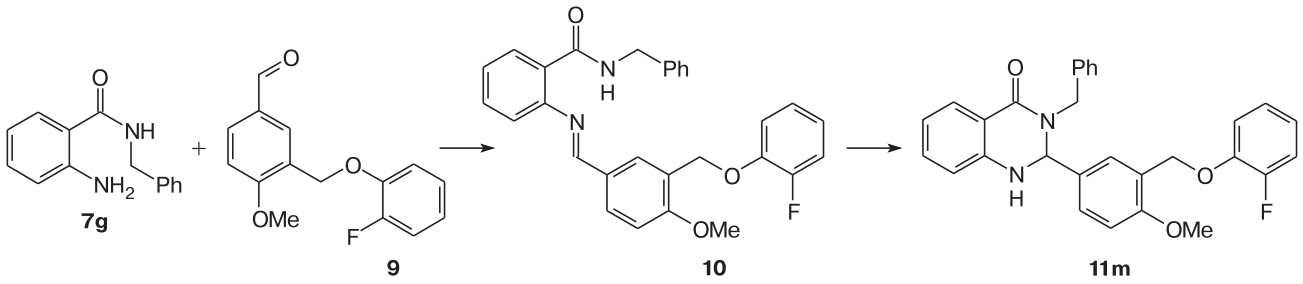
By selection of different solvents, we found conditions (long-term reflux of reagents in a mixture of xylene and acetic acid) under which quinazolinone **11m** was the only reaction product.

The method found can be applied with success for the preparation of numerous quinazolinone derivatives **11a**—**y**, **12a**—**l**, and **13a**,**b** by condensation of the synthesized anthranilic acid amides with aldehydes (including commercially available ones) except for some aldehydes (indolyl, furyl, pyridyl, and pyrazolyl carbaldehydes).

Table 1. Yields, melting points, data from elemental analysis, and ^{1}H NMR spectra for anthranilic acid amides **7a—h** (the solvent was DMSO-d_6 for **7a**,**c**—**g** and $CDCl_3$ for **7b**,**h**)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)		Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H		
7a	67	102	58.61 58.23	5.16 5.43	$C_{10}H_{14}N_2O$	1.00 (t, 3 H, CH_3); 1.65, 3.40 (both m, 2 H each, 2 CH_2); 5.20 (br.s, 2 H, NH_2); 6.20 (br.s, 1 H, NHCO); 6.60—6.80, 7.15—7.35 (both m, 2 H each, CH_{Ar})
7b	82	128—129	60.31 60.45	5.63 5.54	$C_{13}H_{12}N_2O$	5.20 (br.s, 2 H, NH_2); 6.70 (m, 2 H, CH_{Ar}); 7.20—7.70 (m, 7 H, CH_{Ar}); 7.90 (br.s, 1 H, NHCO)
7c	78	147—148	62.01 62.11	6.26 6.12	$C_{14}H_{14}N_2O_2$	3.75 (c, 3 H, OCH_3); 6.30 (br.s, 2 H, NH_2); 6.70—7.60 (m, 8 H, CH_{Ar}); 8.80 (br.s, 1 H, NHCO)
7d	83	97—98	65.32 65.05	6.44 6.06	$C_{13}H_{11}FN_2O$	6.15 (br.s, 2 H, NH_2); 6.34, 6.61 (both m, 1 H each, 2 CH_{Ar}); 7.12 (d, 2 H, CH_{Ar}, *J* = 8.2); 7.20 (m, 1 H, CH_{Ar}); 7.58 (d, 2 H, CH_{Ar}, *J* = 8.2); 7.60 (m, 1 H, CH_{Ar}); 9.76 (br.s, 1 H, NHCO)
7e	77	141	66.85 66.65	6.58 6.71	$C_{14}H_{14}N_2O$	2.26 (c, 3 H, CH_3); 6.30 (br.s, 2 H, NH_2); 6.58 (dd, 1 H, CH_{Ar}, *J* = 8.2, *J* = 1.2); 6.71 (d, 1 H, CH_{Ar}, *J* = 8.2); 7.12 (d, 2 H, CH_{Ar}, *J* = 8.4); 7.20 (dd, 1 H, CH_{Ar}, *J* = 8.2, *J* = 7.9); 7.58 (d, 2 H, CH_{Ar}, *J* = 8.4); 7.60 (m, 1 H, CH_{Ar}); 9.85 (br.s, 1 H, NHCO)
7f	86	84—85	68.25 68.04	7.54 7.22	$C_{12}H_{12}N_2O_2$	4.39 (d, 2 H, CH_2, *J* = 1.9); 6.33, 6.43 (both d, 1 H each, 2 CH_{Fur}, *J* = 3.9); 6.46 (br.s, 2 H, NH_2); 6.50 (t, 1 H, CH_{Ar}, *J* = 9.2); 6.63 (d, 1 H, CH_{Ar}, *J* = 6.7); 7.11 (t, 1 H, CH_{Ar}, *J* = 9.3); 7.41 (d, 1 H, CH_{Ar}, *J* = 6.7); 7.51 (br.s, 1 H, CH_{Fur}); 8.72 (br.s, 1 H, NH)
7g	81	90—91	74.66 74.25	6.01 6.24	$C_{14}H_{14}N_2O$	4.37 (d, 2 H, CH_2, *J* = 2.2); 5.76 (br.s, 2 H, NH_2); 6.55 (d, 1 H, CH_{Ar}, *J* = 7.9); 7.20—7.40 (m, 7 H, CH_{Ar}); 7.65 (d, 1 H, CH_{Ar}, *J* = 7.6); 8.91 (br.s, 1 H, NH)
7h	65	Oil	66.23 66.35	8.88 9.00	$C_{13}H_{21}N_3O$	1.00 (t, 6 H, $(C\underline{H}_3CH_2)_2N$); 2.40—2.70 (m, 6 H, $(CH_3C\underline{H}_2)_2N$ + + $NHCH_2C\underline{H}_2$); 3.50 (m, 2 H, $NHC\underline{H}_2CH_2$); 5.60 (br.s, 2 H, NH_2); 6.60 (m, 2 H, CH_{Ar}); 6.90 (br.s, 1 H, $N\underline{H}CH_2$); 7.20, 7.30 (both m, 1 H each, 2 CH_{Ar})

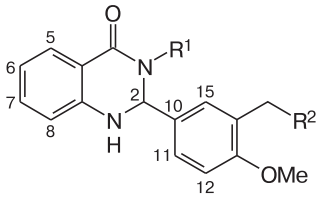
Scheme 3



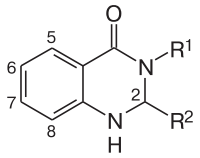
In the case of using indolyl, furyl, pyridyl, and pyrazolyl carbaldehydes, the reaction is completed by the formation of compounds **14** (Scheme 4; sh own by the example of indole-2-carboxaldehyde) due to thermal elimination of the aromatic residue from the 2 position of the quinazolinone ring (*cf.* Ref. 15).

The works[6,7] showed that quinazolinones **5** having alkyl substituents in the 2 position readily undergo alkylation with alkyl halides to form 1-alkyl derivatives. However, our attempts to alkylate 2-aryl quinazolinone **12l** with methyl iodide and to acylate with acetyl chloride and benzoyl chloride were failed, while the reaction with phenyl isocyanate afforded the corresponding carbamide derivative **16** (Scheme 5).

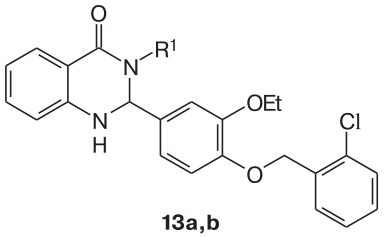
When carboxyl-containing aromatic aldehydes (2-aldobenzoic acids **17a**,**b**) were used in the synthesis of quinazolinones, the reactions were completed by the formation of intramolecular acylation products **18a**,**b** (Scheme 6).



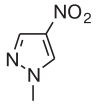
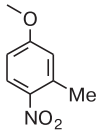
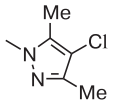
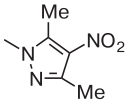
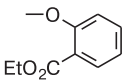
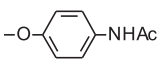
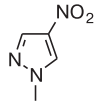
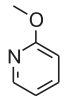
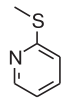
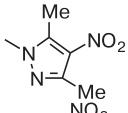
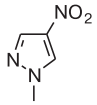
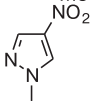
11a—y

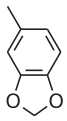
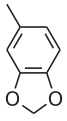
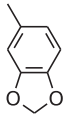
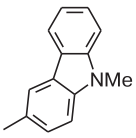


12a—l



13a,b

11	R^1	R^2	**11**	R^1	R^2	**11**	R^1	R^2	**11**	R^1	R^2
a	Ph		**h**	4-$MeOC_6H_4$	2-FC_6H_4O	**n**	Bn		**t**		
b	Ph		**i**	4-FC_6H_4		**o**	Bn		**u**	2-FC_6H_4	2-FC_6H_4O
c	4-$MeOC_6H_4$		**j**	4-MeC_6H_4	2,4,6-$Cl_3C_6H_2O$	**p**	Bn	4-$O_2NC_6H_4O$	**v**	2-FC_6H_4	2,4,6-$Cl_3C_6H_2O$
d	4-FC_6H_4		**k**	4-MeC_6H_4		**q**	Bn	3-$MeOC_6H_4O$	**w**	2-FC_6H_4	2,4,6-$Br_3C_6H_2O$
e	4-$MeOC_6H_4$		**l**	4-MeC_6H_4		**r**		2-FC_6H_4O	**x**	Pr	4-$O_2NC_6H_4O$
f	4-$MeOC_6H_4$		**m**	Bn	2-FC_6H_4O	**s**			**y**	Pr	2-$MeOC_6H_4O$
g	4-$MeOC_6H_4$										

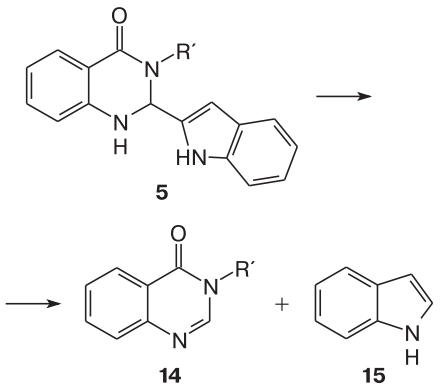
12	R^1	R^2	**12**	R^1	R^2	**12**	R^1	R^2	**12**	R^1	R^2
a	4-FC_6H_4		**d**	Ph	4-FC_6H_4	**g**	4-$MeOC_6H_4$		**j**	$Et_2N(CH_2)_2$	4-ClC_6H_4
b	Bn		**e**	Ph	3-FC_6H_4	**h**	Bn	Ph	**k**	$Et_2N(CH_2)_2$	3-FC_6H_4
c	Ph	2,4-$(MeO)_2C_6H_3$	**f**	4-$MeOC_6H_4$		**i**	Pr	4-FC_6H_4	**l**	Pr	2,4-$(MeO)_2C_6H_3$

13: R^1 =  (**a**), 2-FC_6H_4 (**b**)

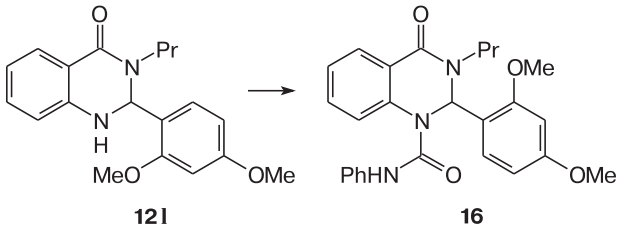
2-Aminobenzhydrazide (**19**) also enters into the analogous reaction with aromatic aldehydes followed by cyclization of the bis-arylmethylidene intermediate **21** into the 2-aryl 3-arylmethylideneamine quinazolinone derivative **22** (Scheme 7).

The structures of all synthesized compounds were established by IR and ^1H and ^{13}C NMR spectroscopy (Tables 2 and 3) and the structures of some compounds were additionally determined by 2D NMR spectroscopy and chromatography-mass spectrometry on a chiral col-

Scheme 4



Scheme 5



umn. The last method also confirmed that the synthesized quinazolinones **11g** and **22d** (2*R*- and 2*S*-isomers) exhibit stereoisomerism[6—18] and exist as racemic mixtures.

The structures of quinazolinones **11g** and **22d** were confirmed by the cumulative ^{1}H and ^{13}C NMR, DEPTq, HSQC, NOESY, COSY, and HMBC spectra. The NOESY correlations for the protons of quinazolinone **11g** are shown in Fig. 1. The H(5) (δ 7.63) and H(7) (δ 7.23) protons typical of this quinazolinone system are downfield shifted with regard to the H(6) and H(8) protons (δ 6.67) whose signal merges into one multiplet and the H(2) proton neighbor to the NH group (d, δ 7.40, $J \approx 2$ Hz) is the most upfield shifted (d, δ 6.10, $J \approx 2$ Hz).

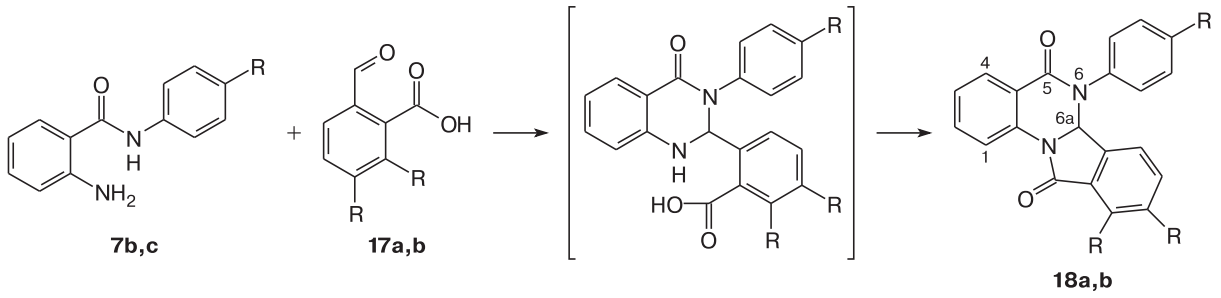
As could be expected, quinazolinone **22d** (see Fig. 1) is in the *anti*-conformation, which is confirmed by the fact that the ^{1}H NMR spectrum contains one signal for the H(22) proton as a singlet at δ 8.77.

The introduction of the hydrazone fragment into the quinazolinone system has no significant effect on the chemical shifts of the H(5)—H(8) protons, which allowed their identification also in other obtained quinazolinones **22a**—**c**,**e**,**f**.

Bioactivit y study of quinazolinones

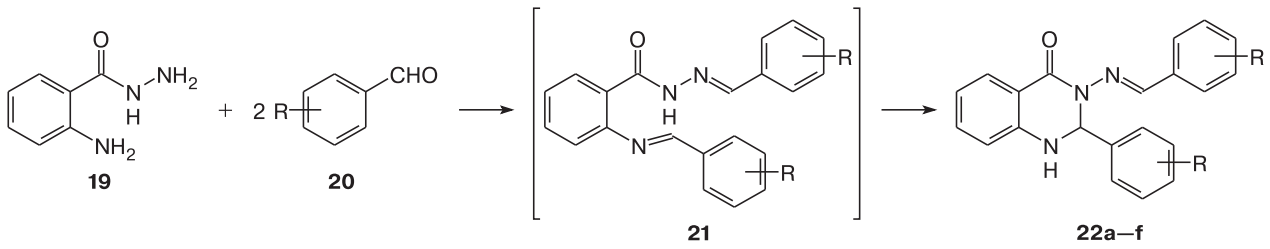
The activity of resulting substances was studied by high-throughput screening (HTS) performed on an automated systems for testing different effects. HTS allows one to rapidly detect and confirm in independent experiments the main effects exerted by the test substance on biochemical processes in living cells.[19]

Scheme 6



R = H (**7b**, **17a**, **18a**), OMe (**7c**, **17b**, **18b**)

Scheme 7



R = 4-Cl (**a**), 4-OMe (**b**), 4-Br (**c**), 2,3-$(MeO)_2$ (**d**), 4-Me (**e**), 3,4-methylenedioxy (**f**)

Table 2. Yields, melting points, data from elemental analysis, and IR and ^{1}H NMR spectra for compounds **11a**—**y**, **12a**—**l**, **13a**,**b**, **16**, and **18a**,**b**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
11a	86	159—160	72.64 72.71	6.42 6.34	9.69 9.78	$C_{26}H_{27}N_3O_3$	3297.6 (N—H), 1004.6—1158.0 (C—O—C, morph.), 1633.1 (C=O), 1611.2 (C_{Ar}=C)	2.11—2.26 (br.t, 4 H, CH_2O_{morph}); 3.33 (br.s, 1 H + H_2O); 3.50 (br.t, 4 H, CH_2N_{morph}, *J* = 4.4); 3.70 (br.s, 3 H, OMe); 6.22 (d, 1 H, 2-Het, *J* = 2.0); 6.66—6.78 (m, 2 H, 6-Het, 8-Het); 6.89 (d, 1 H, CH_{Ar}, *J* = 8.5); 7.12—7.37 (m, 1 H, 7-Het + 8 H, CH_{Ar}); 7.50 (d, 1 H, NH, *J* = 1.9); 7.70 (d, 1 H, 5-Het, *J* = 7.7)
11b	93	159—160	68.53 68.57	5.38 5.33	11.81 11.85	$C_{27}H_{25}N_4O_2Cl$	3285.9 (N—H), 1638.0 (C=O), 1610.9 (C_{Ar}=C), 2838.2 ($C_{Ar}OCH_3$)	1.95, 2.09 (both br.s, 3 H each, 2 Me); 3.76 (br.s, 3 H, OMe); 5.05 (br.s, 2 H, NCH_2); 6.15 (br.s, 1 H, 2-Het); 6.66—6.78 (m, 2 H, 6-Het, 8-Het); 6.89 (d, 1 H, CH_{Ar}, *J* = 8.5); 7.12—7.37 (m, 8 H, 7-Het + 7 CH_{Ar}); 7.46 (d, 1 H, NH, *J* = 1.9); 7.70 (br.d, 1 H, 5-Het, *J* = 7.3)
11c	94	194.5—195.5	71.32 71.36	5.63 5.61	5.22 5.20	$C_{32}H_{30}N_2O_6$	3292.8 (N—H), 2837.7 ($C_{Ar}OCH_3$), 1630.4 (C=O), 1606.1 (C_{Ar}=C)	1.13 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.1); 3.68 (s, 3 H, OCH_3); 3.76 (s, 3 H); 4.20 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.1); 4.98—5.12 (m, 2 H, OCH_2); 6.13 (s, 1 H, 2-Het); 6.65—6.81 (m, 2 H, 6-Het + 8-Het + 2 H, CH_{Ar}); 6.94 (d, 1 H, 12-CH_{Ar}, *J* = 8.8); 6.99—7.13 (m, 4 H, CH_{Ar}); 7.20—7.30 (m, 2 H, 7-Het + CH_{Ar}); 7.38 (br.s, 1 H, NH); 7.43—7.53 (m, 1 H, CH_{Ar}); 7.56 (br.s, 1 H, 15-CH_{Ar}); 7.66 (dd, 1 H, 6-Het, *J* = 7.7, *J* = 1.5); 7.69 (d, 1 H, *o*-CH($ArCO_2Et$), *J* = 8.3)
11d	95	281—282	70.37 70.44	5.11 5.12	8.23 8.21	$C_{30}H_{26}FN_3O_4$	3292.8 (N—H), 2840.6 ($C_{Ar}OCH_2$), 1616.9 (C=O), 1601.9 (C_{Ar}=C)	1.99 (s, 3 H, CH_3CO); 3.71 (s, 3 H, OMe); 6.12 (br.s, 1 H, 2-Het); 6.66—6.77 (m, 2 H, 6-Het, 8-Het); 6.81—6.89, 7.08—7.16 (both m, 2 H each, CH_{Ar}); 7.21—7.31 (m, 1 H, 7-Het + 2 H, CH_{Ar}); 7.40—7.50 (m, 1 H, NH + 2 H, CH_{Ar}); 7.70 (d, 1 H, 5-Het, *J* = 7.5); 9.91 (s, 1 H, CONH)
11e	92	194—195	72.00 71.93	5.33 5.39	8.97 8.99	$C_{28}H_{25}N_3O_4$	3288.6 (N—H), 1626.8 (C—N_{Py}), 1654.6 (C=O), 2836.4 ($C_{Ar}OCH_3$)	3.71, 3.76 (both s, 3 H each, OMe); 4.93 (s, 2 H, OCH_2); 6.08 (d, 1 H, 2-Het, *J* = 2.0); 6.18 (dt, 1 H, 5-CH_{Py}, *J* = 10.0, *J* = 1.3); 6.39 (dd, 1 H, 3-CH_{Py}, *J* = 9.8, *J* = 1.4); 6.65—6.73 (m, 2 H, 6-Het, 8-Het); 6.76—6.83 (m, 2 H, *m*-CH_{ArOMe}); 6.92 (d, 1 H, 12-CH_{Ar}, *J* = 8.5); 6.97 (d, 1 H, 4-CH_{Py}, *J* = 2.1); 7.02—7.09 (m, 2 H, *o*-CH_{ArOMe}); 7.17—7.29 (m, 2 H, 11-CH_{Ar} + + 7-Het); 7.36 (d, 1 H, NH, *J* = 1.9); 7.38—7.46 (m, 2 H, 6-CH_{Py} + 15-CH_{Ar}); 7.63 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.3)
11f	93	198—198.5	65.43 65.49	5.37 5.30	13.66 13.64	$C_{28}H_{27}N_5O_5$	3259.7 (N—H), 2837.3 ($C_{Ar}OCH_3$), 1631.5 (C=O), 1609.9 (C=N), 1561.4 (C_{Ar}=C)	2.34, 2.38 (both s, 3 H each, Me); 3.72, 3.78 (both s, 3 H each, OMe); 5.17 (s, 2 H, CH_2N); 6.04 (d, 1 H, 2-Het, *J* = 2.4); 6.57 (d, 1 H, 15-CH_{Ar}, *J* = 2.1); 6.59—6.67 (m, 2 H, 6-Het, 8-Het); 6.79—6.86 (m, 2 H, *m*-CH_{ArOMe}); 6.96 (d, 1 H, 12-CH_{Ar}, *J* = 8.5); 7.00—7.08 (m, 2 H, *o*-CH_{ArOMe}); 7.16—7.24 (m, 2 H, 11-CH_{Ar}, 7-Het); 7.39 (d, 1 H, NH, *J* = 2.4); 7.56 (dd, 1 H, 5-Het, *J* = 7.9, *J* = 1.3)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
11g	93	229—229.5	64.34 64.32	4.77 4.77	14.45 14.43	$C_{26}H_{23}N_5O_5$	3294.7 (N—H), 2839.1 ($C_{Ar}OCH_3$), 1627.0 (C=O), 1608.6 (C=N), 1509.0 (C_{Ar}=C)	3.71, 3.76 (both s, 3 H each, OMe); 5.28 (s, 2 H, CH_2N); 6.10 (d, 1 H, 2-Het, *J* = 1.9); 6.62—6.72 (m, 2 H, 6-Het, 8-Het); 6.78—6.86 (m, 2 H, *m*-CH_{ArOMe}); 6.95 (d, 1 H, 12-CH_{Ar}, *J* = 8.5); 6.99 (d, 1 H, 15-CH_{Ar}, *J* = 1.9); 7.04—7.12 (m, 2 H, *o*-CH_{ArOMe}); 7.19—7.27 (m, 2 H, 11-CH_{Ar}, 7-Het); 7.39 (d, 1 H, CH_{Ar}, NH, *J* = 1.8); 7.63 (d, 1 H, 5-Het, *J* = 7.6); 8.21 (s, 1 H, 3-CH_{Pyr}); 8.73 (s, 1 H, 5-CH_{Pyr})
11h	92	177—178	71.93 71.89	5.12 5.20	5.73 5.78	$C_{29}H_{25}FN_2O_4$	—	3.70, 3.76 (both s, 3 H each, OMe); 5.04 (s, 2 H, OCH_2); 6.15 (d, 1 H, 2-Het, *J* = 2.1); 6.65—6.74 (m, 2 H, 6-Het, 8-Het); 6.78—6.85 (m, 2 H, *m*-CH_{ArOMe}); 6.89—7.00 (m, 2 H, CH_{Ar}); 7.03—7.15 (m, 4 H, CH_{Ar}); 7.16—7.32 (m, 1 H, 7-Het + 2 H, CH_{Ar}); 7.45 (br.s, 2 H, 15-CH_{Ar}, NH); 7.68 (dd, 1 H, 5-Het, *J* = 7.6, *J* = 1.0)
11i • • HCl	88	183—185	64.62 64.53	5.71 5.62	8.84 8.68	$C_{26}H_{27}ClFN_3O_3$	1608.5; 1506.4 (C_{Ar}=C), 1639.3 (C=O), 3316.9 (N—H), 2849.6 ($C_{Ar}OCH_3$), 1008.4—1153.2 (C—O—C, morph.)	2.05—2.36 (br.s, 2 H, CH_2); 3.33 (br.s, 4 H, CH_2 (morph.)); 3.43—3.65 (m, 4 H, CH_2 (morph.)); 3.73 (s, 3 H, OMe); 6.22 (br.s, 1 H, 2-Het); 6.67—6.80 (m, 2 H, 6-Het, 8-Het); 6.86—6.98 (br.s, 1 H, CH_{Ar}); 7.07—7.17 (m, 2 H, CH_{Ar}); 7.18—7.42 (m, 4 H, 7-Het + NH + 2 CH_{Ar}); 7.47 (br.s, 1 H, 15-CH_{Ar}); 7.64 (br.s, 1 H, 5-Het, *J* = 7.6); 10.39 (br.s, 1 H, NH^+)
11j	92	154—154.5	62.85 62.89	4.22 4.19	5.07 5.06	$C_{29}H_{23}Cl_3N_2O_3$	3297.0 (N—H), 2836.9 ($C_{Ar}OCH_3$), 2940.1 (CH_3), 1632.8 (C=O), 1551.1 (C_{Ar}=C)	2.26 (s, 3 H, Me); 3.69 (s, 3 H, OMe); 4.95 (s, 2 H, OCH_2); 6.18 (d, 1 H, 2-Het, *J* = 2.6); 6.66—6.77 (m, 2 H, 6-Het, 8-Het); 6.95 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.13 (br.s, 5 H, CH_{Ar}); 7.22—7.29 (m, 1 H, 7-Het); 7.32 (dd, 1 H, CH_{Ar}, *J* = 8.5, *J* = 2.3); 7.55 (d, 1 H, NH, *J* = 2.3); 7.58 (d, 1 H, 11-CH_{Ar}, *J* = 2.6); 7.65 (s, 1 H, CH_{Ar}); 7.69 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.4)
11k	94	168—169	66.57 66.51	4.95 4.94	14.94 14.92	$C_{26}H_{23}N_5O_4$	3295.9 (N—H), 2841.4 ($C_{Ar}OCH_3$), 2925.5 (CH_3), 1633.0 (C=O), 1610.6 (C=N), 1504.8 (C_{Ar}=C)	2.24 (s, 3 H, Me); 3.76 (s, 3 H, OMe); 5.27 (s, 2 H, CH_2N); 6.14 (d, 1 H, 2-Het, *J* = 2.3); 6.62—6.73 (m, 2 H, 6-Het, 8-Het); 6.95 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 6.98 (d, 1 H, 15-CH_{Ar}, *J* = 2.2); 7.03—7.12 (m, 4 H, *o*-CH_{ArOMe} + *m*-CH_{ArOMe}); 7.19—7.29 (m, 2 H, 11-CH_{Ar}, 7-Het); 7.44 (d, 1 H, NH, *J* = 2.3); 7.64 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.3); 8.21 (d, 1 H, 3-CH_{Pyr}, *J* = 0.4); 8.71 (s, 1 H, 5-CH_{Pyr})
11l	93	195—196	71.99 71.92	5.42 5.39	8.94 8.99	$C_{28}H_{25}N_3O_2S$	3323.7 (N—H), 2949.0 (CH_3), 2835.2 ($C_{Ar}OCH_3$), 1631.9 (C=O), 1609.2 (C=N), 1578.8 (C_{Ar}=C)	2.23 (s, 3 H, Me); 3.76 (s, 3 H, OMe); 4.26 (s, 2 H, CH_2S); 6.11 (d, 1 H, 2-Het, *J* = 2.3); 6.64—6.72 (m, 2 H, 6-Het, 8-Het); 6.89 (d, 1 H, 12-CH_{Ar}, *J* = 8.3); 6.98—7.06 (m, 4 H, CH_{Ar}); 7.07—7.13 (m, 1 H, 5-CH_{Py}); 7.16—7.28 (m, 1 H, 7-Het + 2 H, CH_{Ar}); 7.43—7.48 (m, 2 H, NH + 15-CH_{Ar}); 7.57—7.64 (m, 1 H, 4-CH_{Py}); 7.65—7.70 (m, 1 H, 5-Het); 8.37—8.41 (m, 1 H, 6-CH_{Py})

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
11m	92	142—142.5	74.40 74.34	5.44 5.38	5.97 5.98	$C_{29}H_{25}FN_2O_3$	3300.0 (N—H), 2839.3 ($C_{Ar}OCH_3$), 1632.8 (C=O), 1610.5 (C=N), 1499.4 (C_{Ar}=C)	3.74 (d, 1 H, $NCH_{2(a)}$, *J* = 15.3); 3.79 (s, 3 H, OMe); 5.05 (s, 2 H, OCH_2); 5.26 (d, 1 H, $NCH_{2(b)}$, *J* = 15.3); 5.68 (d, 1 H, 2-Het, *J* = 2.3); 6.62 (d, 1 H, 8-Het, *J* = 8.0); 6.67 (dt, 1 H, 6-Het, *J* = 7.6, *J* = 1.1); 6.89—6.98 (m, 1 H, CH_{Ar}); 7.02 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.05—7.35 (m, 1 H, 7-Het + 10 H, CH_{Ar}); 7.38 (d, 1 H, NH, *J* = 2.2); 7.68 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.4)
11n	94	189—190	66.44 66.51	4.99 4.94	15.05 14.92	$C_{26}H_{23}N_5O_4$	3292.4 (N—H), 2840.6 ($C_{Ar}OCH_3$), 999.8 (N—O), 1635.4 (C=O), 1611.5 (C=N), 1524.8 (C_{Ar}=C)	3.74 (d, 1 H, $NCH_{2(a)}$, *J* = 15.3); 3.81 (s, 3 H, OCH_3); 5.21 (d, 1 H, $NCH_{2(b)}$, *J* = 15.3); 5.28 (s, 2 H, CH_2N_{Pyr}); 5.61 (d, 1 H, 2-Het, *J* = 2.4); 6.54 (d, 1 H, 8-Het, *J* = 8.1); 6.64 (br.t, 1 H, 6-Het, *J* = 7.8); 6.88 (d, 1 H, CH_{Ar}, *J* = 2.0); 7.01 (d, 1 H, 12-CH_{Ar}, *J* = 8.5); 7.15—7.36 (m, 7 H, 7-Het + NH + 5 CH_{Ar}); 7.62 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.4); 8.19 (s, 1 H, 3-CH_{Pyr}); 8.77 (s, 1 H, 5-CH_{Pyr})
11o	93	244—245	67.57 67.59	5.50 5.47	14.06 14.08	$C_{28}H_{27}N_5O_4$	3272.1 (N—H), 2843.8 ($C_{Ar}OCH_3$), 1621.6 (C=O), 1611.9 (C=N), 1562.5 (C_{Ar}=C), 2930.5 (CH_3)	2.37 (s, 6 H, 2 Me); 3.71 (d, 1 H, $NCH_{2(a)}$, *J* = 15.3); 3.81 (s, 3 H, OMe); 5.09—5.26 (m, 3 H, $NCH_{2(b)}$ + CH_2N_{Pyr}); 5.57 (d, 1 H, 2-Het, *J* = 2.4); 6.49 (d, 1 H, 15-CH_{Ar}, *J* = 2.1); 6.54 (d, 1 H, 8-Het, *J* = 8.1); 6.59 (dt, 1 H, 6-Het, *J* = 7.5, *J* = 1.1); 7.01 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.11—7.36 (m, 8 H, 7-Het + NH + 6 CH_{Ar}); 7.55 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.4)
11p	93	170—171	70.24 70.29	5.15 5.09	8.57 8.48	$C_{29}H_{25}N_3O_5$	3311.5 (N—H), 2841.3 ($C_{Ar}OCH_3$), 1624.9 (C=O), 1592.4 (C_{Ar}=C), 994.0 (N—O)	3.72—3.84 (m, 4 H, CH_3 + $NCH_{2(a)}$); 5.15 (s, 2 H, OCH_2); 5.25 (d, 1 H, $NCH_{2(b)}$, *J* = 15.4); 5.68 (d, 1 H, 2-Het, *J* = 2.3); 6.60 (d, 1 H, 8-Het, *J* = 8.0); 6.66 (br.t, 1 H, 6-Het, *J* = 7.5); 7.03 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.10—7.16 (m, 2 H, *m*-CH($ArNO_2$)); 7.16—7.38 (m, 9 H, 7-Het + NH + 7 CH_{Ar}); 7.65 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.2); 8.15—8.23 (m, 2 H, *o*-CH($ArNO_2$))
11q	95	144—145	74.96 74.98	5.93 5.87	5.82 5.83	$C_{30}H_{28}N_2O_4$	3296.3 (N—H), 2835.7 ($C_{Ar}OCH_3$), 1624.9 (C=O), 1614.5; 1582.5 (C_{Ar}=C), 2928.6 (CH_2)	3.73 (s, 3 H, OMe); 3.75—3.82 (m, 3 H, OMe + 1 H, $NCH_{2(a)}$); 4.96 (s, 2 H, OCH_2); 5.26 (d, 1 H, $NCH_{2(b)}$, *J* = 15.4); 5.67 (d, 1 H, 2-Het, *J* = 2.0); 6.47—6.56 (m, 3 H, CH_{Ar}); 6.63 (d, 1 H, 8-Het, *J* = 8.1); 6.68 (br.t, 1 H, 6-Het, *J* = 7.5); 7.00 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.13—7.36 (m, 9 H, 7-Het + 8 CH_{Ar}); 7.39 (d, 1 H, NH, *J* = 1.9); 7.69 (br.d, 1 H, 5-Het, *J* = 7.6)
11r	94	118—119	70.76 70.73	4.69 5.06	6.07 6.11	$C_{27}H_{23}FN_2O_4$	3066.8 (C—H, furan), 1611.3 (C—C, furan), 1634.7 (C=O), 3305.5 (N—H)	3.75—3.87 (m, 3 H, OCH_3 + 1 H, $CH_{2(a)}N$); 5.06 (s, 2 H, OCH_2); 5.15 (d, 1 H, $CH_{2(b)}N$, *J* = 15.1); 5.71 (d, 1 H, 2-Het, *J* = 2.3); 6.26 (d, 1 H, 3-CH_{Fur}); 6.35—6.38 (m, 1 H, 4-CH_{Fur}); 6.61 (d, 1 H, 8-Het, *J* = 8.1); 6.63—6.70 (m, 1 H, 6-Het); 6.89—6.99 (m, 1 H, CH_{Ar}); 7.02 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.05—7.13 (m, 1 H, CH_{Ar}); 7.13—7.22 (m, 3 H, 7-Het + 2 CH_{Ar}); 7.22—7.32 (m, 2 H, NH + CH_{Ar}); 7.39 (d, 1 H, 15-CH_{Ar}, *J* = 2.4); 7.54—7.57 (m, 1 H, CH_{Ar}); 7.66 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.4)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
11s	90	125—126	62.73 62.74	4.63 4.61	15.20 15.24	$C_{24}H_{21}N_5O_5$	3276.1 (N—H), 3123.8 (C—H, furan), 2840.2 ($C_{Ar}OCH_3$), 1612.3 (C—C, furan), 1626.1 (C=O), 1581.2 (C=N), 1503.2 (C_{Ar}=C)	3.79 (s, 3 H, OMe); 3.83 (d, 1 H, $NCH_{2(a)}$, *J* = 15.6); 5.15 (d, 1 H, $NCH_{2(b)}$, *J* = 15.6); 5.30 (d, 2 H, CH_2N_{Pyr}, *J* = 2.0); 5.65 (d, 1 H, 2-Het, *J* = 2.1); 6.26 (d, 1 H, 3-CH_{Fur}, *J* = 3.1); 6.34—6.39 (m, 1 H, 4-CH_{Fur}); 6.57 (d, 1 H, 8-Het, *J* = 8.0); 6.63 (br.t, 1 H, 6-Het, *J* = 7.4); 6.89 (d, 1 H, 5-CH_{Fur}, *J* = 2.0); 7.01 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.18 (dt, 1 H, 7-CH_{Ar}, *J* = 7.7, *J* = 1.6); 7.22—7.28 (m, 2 H, 11-CH_{Ar}, 15-CH_{Ar}); 7.55 (d, 1 H, NH, *J* = 1.0); 7.60 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.2); 8.19 (s, 1 H, 3-CH_{Pyr}); 8.77 (s, 1 H, 5-CH_{Pyr})
11t	91	163—164	67.29 67.33	5.10 5.04	8.45 8.41	$C_{28}H_{25}N_3O_6$	3074.1 (C—H, furan), 1610.8 (C—C, furan), 2937.3 (CH_2), 3303.2 (N—H), 2838.4 ($C_{Ar}OCH_3$), 3010.5 (CH_3)	2.54 (s, 3 H, CH_3); 3.79 (s, 3 H, OCH_3); 3.83 (d, 1 H, $NCH_{2(a)}$, *J* = 15.6); 5.12 (s, 2 H, CH_2O); 5.14 (d, 1 H, $NCH_{2(b)}$, *J* = 15.6); 5.65 (d, 1 H, 2-Het, *J* = 2.1); 6.27 (d, 1 H, 3-CH_{Fur}, *J* = 3.1); 6.37 (d, 1 H, 4-CH_{Fur}, *J* = 3.1); 6.58 (d, 1 H, 8-Het, *J* = 8.0); 6.65 (t, 1 H, 6-Het, *J* = 7.4); 6.97 (d, 1 H, *J* = 2.0); 7.01—7.38 (m, 6 H, 7-Het + 5 CH_{Ar}); 7.56 (d, 1 H, NH, *J* = 1.0); 7.62 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.2); 8.19 (d, 1 H, *m*-$CH(ArNO_2)$, *J* = 8.0)
11u	94	129—130	71.15 71.18	4.76 4.69	5.87 5.93	$C_{28}H_{22}F_2N_2O_3$	3297.7 (N—H), 2840.2 ($C_{Ar}OCH_3$), 1590.7 (C=O)	2.08 (s, 3 H, Me); 3.76 (s, 3 H, OMe); 5.02 (s, 2 H, CH_2O); 6.19 (br.s, 1 H, 2-Het); 6.71—6.81 (m, 2 H, 6-Het, 8-Het); 6.89—7.06 (m, 3 H, CH_{Ar}); 7.07—7.30 (m, 6 H, 7-Het + 5 CH_{Ar}); 7.31—7.37 (m, 2 H, CH_{Ar}); 7.41 (br.s, 1 H, 15-CH_{Ar}); 7.51 (d, 1 H, NH, *J* = 2.2); 7.67 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.4)
11v	92	160—161.5	60.37 60.29	3.55 3.61	4.92 5.02	$C_{28}H_{20}FCl_3N_2O_3$	1635.3 (C=O), 1609.1 (C_{Ar}=C), 3294.9 (N—H)	3.69 (s, 3 H, OCH_3); 4.93 (br.s, 2 H, OCH_2); 6.20 (br.s, 1 H, 2-Het); 6.71—6.82 (m, 2 H, 6-Het, 8-Het); 6.93 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.04—7.39 (m, 6 H, 7-Het +5 CH_{Ar}); 7.46 (br.s, 1 H, 15-CH_{Ar}); 7.60 (d, 1 H, NH, *J* = 2.2); 7.67 (s, 2 H, *m*-CH_{ArCl}); 7.70 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.6)
11w	93	166—167	48.63 48.66	2.95 2.92	4.04 4.05	$C_{28}H_{20}Br_3FN_2O_3$	1372.7 (C—F), 1635.3 (C=O), 1609.4 (C_{Ar}=C), 3291.9 (N—H)	3.71 (s, 3 H, OMe); 4.83—4.96 (m, 2 H, OCH_2); 6.20 (br.s, 1 H, 2-Het); 6.30—6.70 (m, 2 H, 6-Het, 8-Het); 6.93 (d, 1 H, 12-CH_{Ar}, *J* = 8.8); 7.04—7.38 (m, 6 H, 7-Het + 5 CH_{Ar}); 7.45 (br.s, 1 H, CH_{Ar}); 7.66 (d, 1 H, NH, *J* = 2.0); 7.71 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.0); 7.65 (s, 2 H, *m*-CH_{ArBr})
11x	88	175—176	67.13 67.10	5.61 5.63	9.36 9.39	$C_{25}H_{25}N_3O_5$	1619.5 (C_{Ar}=C), 1639.4 (C=O), 2838.2 ($C_{Ar}OCH_3$), 2965.3 (CH_2), 3292.6 (N—H)	0.80 (t, 3 H, γ-Me (Pr), *J* = 7.3); 1.40—1.62 (m, 2 H, β-Me); 2.60—2.74 (m, 1 H, α-$CH_{2(a)}$); 3.70—3.80 (m, 1 H, α-$CH_{2(b)}$); 3.81 (s, 3 H, OCH_3); 5.18 (s, 2 H, OCH_2); 5.79 (d, 1 H, 2-Het, *J* = 2.0); 6.55—6.70 (m, 2 H, 6-Het, 8-Het); 7.05 (d, 1 H, 12-CH_{Ar}, *J* = 8.6); 7.11—7.19 (m, 2 H, *o*-$CH(ArNO_2)$ + 1 H, 11-CH_{Ar}); 7.25—7.33 (m, 2 H, 15-CH_{Ar}, 7-Het); 7.39 (d, 1 H, NH, *J* = 2.2); 7.61 (dd, 1 H, 5-Het, *J* = 7.9, *J* = 1.3); 8.21 (m, 2 H, *m*-$CH(ArNO_2)$)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d^6), δ (*J*/Hz)
11y	86	111.5—112	72.23 72.20	6.49 6.52	6.54 6.48	$C_{26}H_{28}N_2O_4$	2834.6 ($C_{Ar}OCH_3$), 2935.2; 2959.9 (CH_2), 3297.9 (N—H), 1621.9 (C_{Ar}=C), 1665.2 (C=O)	0.80 (t, 3 H, γ-Me (Pr), *J* = 7.8); 1.48 (m, 2 H, β-CH_2); 2.68, 3.70 (both m, 1 H each, α-CH_2); 3.72, 3.79 (both s, 3 H each, OCH_3); 4.97 (s, 2 H, OCH_2); 5.79 (d, 1 H, 2-Het, *J* = 2.1); 6.47—6.55 (m, 3 H, CH_{Ar}); 6.59—6.68 (m, 2 H, 6-Het, 8-Het); 7.01 (d, 1 H, 12-CH_{Ar}, *J* = 8.5); 7.11—7.22 (m, 2 H, 7-Het + CH_{Ar}); 7.26 (br.s, 2 H, CH_{Ar}); 7.43 (d, 1 H, NH, *J* = 2.1); 7.63 (d, 1 H, 5-Het, *J* = 7.5)
12a	93	272.5—273	69.63 69.61	4.15 4.17	7.71 7.73	$C_{21}H_{15}FN_2O_3$	933.3 (C—O—C, benzodioxole), 1611.3; 1502.0 (C_{Ar}=C), 1639.3 (C=O), 3297.9 (N—H)	5.97 (d, 2 H, OCH_2O, *J* = 2.7); 6.19 (d, 1 H, 2-Het, *J* = 2.1); 6.69—6.78 (m, 2 H, 6-Het, 8-Het); 6.80 (br.s, 2 H, CH_{Ar}); 6.93 (br.s, 1 H, CH_{Ar}); 7.10—7.20 (m, 2 H, CH_{Ar}); 7.21—7.33 (m, 1 H, 7-Het + 2 H, CH_{Ar}); 7.49 (d, 1 H, NH, *J* = 2.1); 7.71 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.3)
12b	95	176—176.5	73.68 73.73	5.09 5.06	7.84 7.82	$C_{22}H_{18}N_2O_3$	929.3 (C—O—C, benzodioxole), 1610.6; 1501.1 (C_{Ar}=C), 3319.7 (N—H), 1628.1 (C=O)	3.83, 5.27 (both d, 1 H each, NCH_2Ph, *J* = 15.3); 5.67 (d, 1 H, 2-Het, *J* = 2.4); 5.98 (s, 2 H, OCH_2O); 6.61—6.72 (m, 4 H, CH_{Ar}); 6.75 (dd, 1 H, CH_{Ar}, *J* = 8.1, *J* = 1.6); 6.82—6.88 (m, 1 H, NH + 6 H, CH_{Ar}); 7.69 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.4)
12c	91	169—170.5	73.41 73.32	5.52 5.59	7.75 7.77	$C_{22}H_{20}N_2O_3$	3360.8 (N—H), 2840.4 ($C_{Ar}OCH_3$), 1654.4 (C=O), 1611.5 (C_{Ar}=C)	3.69 (s, 3 H, *p*-$ArOCH_3$); 3.74 (s, 3 H, *o*-$ArOCH_3$); 6.32 (d, 1 H, CH_{Ar}, *J* = 2.5); 6.43 (dd, 1 H, CH_{Ar}, *J* = 8.5, *J* = 2.3); 6.52 (d, 1 H, 2-Het, *J* = 2.5); 6.70 (t, 1 H, 8-Het, *J* = 7.5); 6.77 (d, 1 H, 6-Het, *J* = 8.1); 7.11 (d, 1 H, CH_{Ar}, *J* = 2.2); 7.12—7.25 (m, 1 H, 7-Het + 4 H, CH_{Ar}); 7.26—7.36 (m, 2 H, NH + CH_{Ar}); 7.73 (d, 1 H, 5-Het, *J* = 7.8)
12d	93	229.5—230.5	75.39 75.46	4.77 4.75	8.75 8.80	$C_{20}H_{15}FN_2O$	3293.1 (N—H), 1629.0 (C=O), 1605.4 (C_{Ar}=C)	6.31 (d, 1 H, 2-Het, *J* = 2.4); 6.68—6.80 (m, 2 H, 6-Het, 8-Het); 7.08—7.19 (m, 2 H, CH_{Ar}); 7.20—7.28 (m, 1 H, 7-Het + 2 H, CH_{Ar}); 7.29—7.37 (m, 3 H, CH_{Ar}); 7.38—7.45 (m, 2 H, CH_{Ar}); 7.61 (d, 1 H, NH, *J* = 2.3); 7.72 (dd, 1 H, 5-Het, *J* = 1.3, *J* = 7.8)
12e	89	191—191.5	75.44 75.46	4.78 4.75	8.79 8.80	$C_{20}H_{15}FN_2O$	3297.6 (N—H), 1636.0 (C=O), 1609.8 (C_{Ar}=C)	6.34 (d, 1 H, 2-Het, *J* = 2.6); 6.73 (t, 1 H, 6-Het, *J* = 7.9); 6.78 (d, 1 H, 8-Het, *J* = 8.1); 7.04—7.14 (m, 1 H, CH_{Ar}); 7.15—7.40 (m, 1 H, 7-Het + 8 H, CH_{Ar}); 7.69 (d, 1 H, NH, *J* = 2.8); 7.73 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.1)
12f	92	225.5—226	77.53 77.58	5.33 5.35	9.64 9.69	$C_{28}H_{23}N_3O_2$	2831.4 ($C_{Ar}OCH_3$), 3305.5 (N—H), 1633.0 (C=O), 1603.5 (C_{Ar}=C)	3.65 (s, 3 H, OMe); 3.82 (s, 3 H, NMe); 6.38 (d, 1 H, 2-Het, *J* = 1.8); 7.68—7.77 (m, 2 H, 6-Het, 8-Het); 7.78—7.84 (m, 2 H, *m*-CH_{ArOMe}); 7.13—7.22 (m, 3 H, CH_{Ar}); 7.23—7.31 (dt, 1 H, 7-Het, *J* = 7.6, *J* = 1.7); 7.41—7.48 (m, 1 H, CH_{Ar}); 7.51 (br.s, 1 H, NH + 2 H, CH_{Ar}); 7.56 (d, 1 H, CH_{Ar}, *J* = 8.1); 7.76 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.3); 8.04 (d, 1 H, CH_{Ar}, *J* = 7.7); 8.11 (br.s, 1 H, CH_{Ar})

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
12g	94	243—244	70.65 70.58	4.93 4.85	7.40 7.48	$C_{22}H_{18}N_2O_4$	2898.7 ($C_{Ar}OCH_3$), 3291.6 (N—H), 1632.6 (C=O), 1605.4 (C_{Ar}=C)	3.72 (s, 3 H, OMe); 5.96 (dd, 2 H, OCH_2O, *J* = 4.2, *J* = 0.8); 6.11 (d, 1 H, 2-Het, *J* = 2.3); 6.67—6.77 (m, 2 H, 6-Het, 8-Het); 6.79 (br.s, 2 H, CH_{Ar}); 6.84—6.93 (m, 3 H, CH_{Ar}); 7.10—7.18 (m, 2 H, *o*-CH_{ArOMe}); 7.27 (dt, 1 H, 7-Het, *J* = 7.7, *J* = 1.5); 7.44 (d, 1 H, NH, *J* = 2.2); 7.70 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.4)
12h	88	162—163	80.21 80.23	5.76 5.77	8.89 8.91	$C_{21}H_{18}N_2O$	3400.0 (N—H), 1631.9 (C=O), 1618.5 (C_{Ar}=C)	3.82 (d, 1 H, $NCH_{2(a)}$, *J* = 15.4); 5.32 (d, 1 H, $NCH_{2(b)}$, *J* = 15.4); 5.74 (d, 1 H, 2-Het, *J* = 2.6); 6.59—6.73 (m, 2 H, 6-Het, 8-Het); 7.17—7.41 (m, 12 H, 7-Het + NH + 10 CH_{Ar}); 7.69 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.5)
12i	90	154—155	71.86 71.81	6.01 6.03	9.85 9.85	$C_{17}H_{17}FN_2O$	3298.3 (N—H), 1605.2; 1589.8 (C_{Ar}=C), 1626.5 (C=O), 2970.6 (CH_2)	0.83 (t, 3 H, γ-Me (Pr), *J* = 7.2); 1.36—1.65 (m, 2 H, β-CH_2); 2.65—2.77, 3.75—3.88 (both m, 1 H each, α-CH_2); 5.86 (d, 1 H, 2-Het, *J* = 2.3); 6.59—6.69 (m, 2 H, 6-Het, 8-Het); 7.13—7.23 (m, 1 H, 7-Het + 2 H, *m*-CH_{ArF}); 7.30—7.40 (m, 1 H, NH + 2 H, *o*-CH_{ArF}); 7.64 (d, 1 H, 5-Het, *J* = 7.7)
12j	87	116.5—117	67.16 67.12	6.72 6.76	11.75 11.74	$C_{20}H_{24}ClN_3O$	—	0.90 (t, 6 H, $CH_2C\underline{H}_3$, *J* = 7.1); 2.33—2.48 (m, 5 H, β-$CH_{2(b)}$, $C\underline{H}_2CH_3$); 2.53—2.67 (m, 1 H, β-$CH_{2(a)}$); 2.76—2.90 (m, 1 H, α-$CH_{2(b)}$); 3.75—3.87 (m, 1 H, α-$CH_{2(a)}$); 5.97 (d, 1 H, 2-Het, *J* = 2.3); 6.57—6.68 (m, 2 H, 6-Het, 8-Het); 7.19 (dd, 1 H, 7-Het, *J* = 7.8, *J* = 1.5); 7.31 (d, 1 H, NH, *J* = 2.1); 7.35 (d, 2 H, *o*-CH_{Ar}, *J* = 8.5); 7.43 (d, 2 H, *m*-CH_{Ar}, *J* = 8.5); 7.59—7.67 (m, 1 H, 5-Het)
12k	85	106.5—107	70.43 70.36	7.01 7.08	12.35 12.31	$C_{20}H_{24}FN_3O$	—	0.91 (t, 6 H, $CH_2C\underline{H}_3$, *J* = 7.1); 2.33—2.48 (m, 5 H, β-$CH_{2(b)}$, $C\underline{H}_2CH_3$); 2.54—2.67 (m, 1 H, β-$CH_{2(a)}$); 2.80—2.92 (m, 1 H, α-$CH_{2(b)}$); 3.79—3.91 (m, 1 H, α-$CH_{2(a)}$); 5.98 (d, 1 H, 2-Het, *J* = 2.3); 5.98—6.65 (m, 2 H, 6-Het, 8-Het); 7.09—7.25 (m, 4 H, 7-Het, CH_{Ar}); 7.31—7.46 (m, 2 H, CH_{Ar}, NH); 7.59—7.68 (m, 1 H, 5-Het)
12l	88	161—162	69.86 69.92	6.81 6.79	8.62 8.58	$C_{19}H_{22}N_2O_3$	—	0.83 (t, 3 H, γ-Me (Pr), *J* = 7.2); 1.36—1.65 (m, 2 H, β-CH_2); 2.65—2.77 (m, 1 H, α-CH_2); 3.69 (s, 3 H, *p*-$ArOCH_3$); 3.74 (s, 3 H, *o*-$ArOCH_3$); 3.75—3.88 (m, 1 H, α-CH_2); 5.81 (d, 1 H, 2-Het, *J* = 2.1); 6.30 (d, 1 H, CH_{Ar}, *J* = 2.5); 6.41 (dd, 1 H, CH_{Ar}, *J* = 8.4, *J* = 2.3); 6.59—6.69 (m, 2 H, 6-Het, 8-Het); 7.11 (d, 1 H, CH_{Ar}, *J* = 2.4); 7.14—7.19 (m, 1 H, 7-Het); 7.32 (d, 1 H, NH, *J* = 2.2); 7.58 (d, 1 H, 5-Het, *J* = 7.8)
13a	92	112—113	68.76 68.78	5.21 5.15	5.76 5.73	$C_{28}H_{25}ClN_2O_4$	3306.0 (N—H), 2927.6 (CH_3), 2980.2 (CH_2), 3061.1 (C—H, furan),	1.27 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.3); 3.89—4.00 (m, 2 H, $OC\underline{H}_2CH_3$ + 1 H, $NCH_{2(a)}$); 5.07—5.17 (m, 2 H, OCH_2 + 1 H, $NCH_{2(b)}$); 5.71 (d, 1 H, 2-Het, *J* = 2.0); 6.28 (d, 1 H, 3-CH_{Fur}, *J* = 3.2); 6.35—6.40 (m, 1 H, 4-CH_{Fur}); 6.60—6.71 (m, 2 H, 6-Het,

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
13a							1610.9 (C—C, furan), 1632.8 (C=O)	8-Het); 6.78 (dd, 1 H, CH_{Ar}, *J* = 8.3, *J* = 1.9); 6.94—7.01 (m, 2 H, CH_{Ar}); 7.21 (dt, 1 H, 7-Het, *J* = 7.6, *J* = 1.6); 7.28 (d, 1 H, NH, *J* = 2.0); 7.33—7.41 (m, 2 H, CH_{Ar}); 7.45—7.52 (m, 1 H, CH_{Ar}); 7.53—7.58 (m, 2 H, CH_{Ar}); 7.67 (dd, 1 H, 5-Het, *J* = 7.8, *J* = 1.3)
13b	89	198—198.5	69.33 69.25	4.79 4.81	5.54 5.57	$C_{29}H_{24}ClFN_2O_3$	3301.1 (N—H), 1637.4 (C=O), 1609.9 (C=N), 1501.3 (C_{Ar}=C)	1.24 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.3); 4.20 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.3); 5.07 (s, 2 H, OCH_2); 6.20 (br.s, 1 H, CH_{Ar}); 6.65—7.60 (m, 1 H, NH + 14 H, CH_{Ar}); 7.70 (d, 1 H, 5-Het, *J* = 8.1)
16	87	178—179	70.03 70.09	6.17 6.11	9.41 9.43	$C_{26}H_{27}N_3O_4$	1633.7 (C_{Ar}=C), 1683.5 (C=O), 2837.6 ($C_{Ar}OCH_3$), 2965.8 (CH_2), 3230.8 (N—H)	0.85 (t, 3 H, γ-Me (Pr), *J* = 7.3); 1.47—1.72 (m, 2 H, β-CH_2); 2.80—2.94 (m, 1 H, α-$CH_{2(a)}$); 3.78, 3.84 (both s, 3 H each, OMe); 3.87—4.01 (m, 1 H, α-$CH_{2(b)}$); 6.33 (dd, 1 H, 2-Het, *J* = 7.8, *J* = 1.1); 6.87 (t, 1 H, 6-Het, *J* = 8.0); 6.96 (dd, 1 H, 8-Het, *J* = 8.0, *J* = 1.3); 7.05 (t, 1 H, CH_{Ar}, *J* = 7.3); 7.20—7.36 (m, 5 H, CH_{Ar}); 7.41—7.52 (m, 3 H, CH_{Ar}); 7.88 (dd, 1 H, 5-Het, *J* = 7.7, *J* = 1.4); 8.88 (s, 1 H, NH)
18a	83	198—199	77.23 77.29	4.37 4.32	8.50 8.58	$C_{21}H_{14}N_2O_2$	1719.4 (C=O), 1654.4 (C_{Ar}=C), 1364.3 (C—N)	6.10 (d, 1 H, CH_{Ar}, *J* = 7.7); 7.02 (s, 1 H, 2-Het); 7.35—7.45 (m, 3 H, CH_{Ar}); 7.45—7.53 (m, 2 H, CH_{Ar}); 7.57 (t, 2 H, CH_{Ar}, *J* = 7.5); 7.73—7.82 (m, 1 H, CH_{Ar}); 7.89 (d, 1 H, CH_{Ar}, *J* = 7.5); 8.04 (dd, 1 H, 5-Het, *J* = 1.2, *J* = 7.8); 8.12 (d, 1 H, *J* = 8.1)
18b	75	224—225	69.18 69.22	4.86 4.84	6.77 6.73	$C_{24}H_{20}N_2O_5$	2834.9 ($C_{Ar}OCH_3$), 1709.9, 1665.2 (C=O), 1602.9 (C_{Ar}=C), 1349.6 (C—N)	3.78, 3.82, 3.90 (all s, 3 H each, OMe); 5.85 (d, 1 H, CH_{Ar}, *J* = 8.3); 6.73 (br.s, 1 H, *m*-CH_{Ar}); 6.80 (s, 1 H, 2-Het); 6.89 (br.s, 1 H, *m*-$CH_{Ar'}$); 7.10 (d, 1 H, CH_{Ar}, *J* = 8.5); 7.13 (br.s, 1 H, *o*-CH_{Ar}); 7.38 (t, 1 H, 6-Het, *J* = 7.6); 7.68 (br.s, 1 H, *o*-$CH_{Ar'}$); 7.74 (t, 1 H, 7-Het, *J* = 7.8); 8.01 (d, 1 H, 8-Het, *J* = 7.8); 8.08 (d, 1 H, 5-Het, *J* = 8.0)

The SAR analysis allows one to determine chemical groups responsible for different biological effects *in vivo*.[20]

The above-mentioned methods allow one to determine both potentially useful properties of new molecules and possible negative consequences of their use in the disease treatment. The results of the bioactivity studies of quinazolinone derivatives by the above-mentioned methods are specified in the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/).

In our case, compounds **11** and **18** are racemates.

According to the data from the studies performed, compound **11k** (Pubchem CID 2888389) possesses the highest bioactivity. Compound **11k** inhibits the aldehyde dehydrogenase ALDH1A1, which can decrease the rate of malignancy growth of tumor cells, as well as can block the KCNK3 potassium channel causing a decrease in the proliferative activity of tumor cells. In addition, compound **11k** stimulates the expression of the *Rab9* gene encoding the protein responsible for the vesicular transport from endosomes to the Goldgi apparatus.[21] The activity of this protein increases the rate of propagation of low-molecular-weight substances, including drugs, within a cell, which can increase the sensitivity of tumor cells to therapy. Finally, compound **11k** stimulates the function of the SWI/SNF complex, which retards division processes and prevents the action of oncoproteins.

Quinazolinone **11k** increases the expression level of the *NPC1* gene which is fixed in the membranes of endosomes and exosomes and mediates the intracellular transport of cholesterol and lipoproteins. Defects in this gene favor the development of neurogenerative diseases, such as the Niemann—Pick disease and, possibly, the Alzheimer

Table 3. Yields, melting points, data from elemental analysis, and IR and ^{1}H NMR spectra for aryl quinazolinones **22a—f**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula	IR spectrum, ν/cm^{-1}	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)
22a	88	192—192.5	63.60 63.65	3.89 3.82	10.57 10.60	$C_{21}H_{15}Cl_2N_3O$	3321.9 (N—H), 1632.1 (C=O), 1610.7 (C=N), 1503.9 (C_{Ar}=C)	6.51 (d, 1 H, 2-Het, *J* = 3.1); 6.75 (t, 1 H, 6-Het, *J* = 7.5); 6.81 (d, 1 H, 8-Het, *J* = 8.1); 7.26—7.34 (m, 1 H, CH_{Ar}); 7.35—7.45 (m, 4 H, CH_{Ar}); 7.47—7.54 (m, 2 H, CH_{Ar}); 7.68—7.75 (m, 3 H, CH_{Ar}); 7.92 (d, 1 H, NH, *J* = 3.0); 8.90 (s, 1 H, N=CH)
22b	84	224—225	71.33 71.30	5.53 5.46	10.79 10.85	$C_{23}H_{21}N_3O_3$	1504.0 (C_{Ar}=C), 1605.5 (C=N), 1625.4 (C=O), 2838.6 ($C_{Ar}OCH_3$), 3331.8 (N—H)	3.68, 3.79 (both s, 3 H each, OMe); 6.37 (d, 1 H, 2-Het, *J* = 2.6); 6.73 (t, 1 H, 6-Het); 6.78 (d, 1 H, 8-Het, *J* = 8.1); 6.84—6.91 (m, 2 H); 6.96—7.03 (m, 2 H, CH_{Ar}); 7.24—7.33 (m, 3 H, CH_{Ar}); 7.61—7.68 (m, 2 H, CH_{Ar}); 7.70 (dd, 1 H, CH_{Ar}, *J* = 7.8, *J* = 1.3); 7.74 (d, 1 H, NH, *J* = 2.7); 8.75 (s, 1 H, N=CH)
22c	90	206—207	52.03 51.99	3.05 3.12	8.74 8.66	$C_{21}H_{15}Br_2N_3O$	1508.1 (C_{Ar}=C), 1587.7 (C=O), 1611.0 (C=N), 3318.3 (N—H)	6.50 (d, 1 H, 2-Het, *J* = 2.5); 6.75 (t, 1 H, 6-Het, *J* = 7.0); 6.81 (d, 1 H, 8-Het, *J* = 8.5); 7.27—7.37 (m, 3 H, CH_{Ar}); 7.51—7.57 (m, 2 H, CH_{Ar}); 7.66 (s, 4 H, CH_{Ar}); 7.72 (d, 1 H, CH_{Ar}, *J* = 8.5); 7.93 (d, 1 H, NH, *J* = 2.3); 8.88 (s, 1 H, N=CH)
22d	77	170—171	67.03 67.10	5.71 5.63	9.43 9.39	$C_{25}H_{25}N_3O_5$	3349.4 (N—H), 2831.9 ($C_{Ar}OCH_3$), 1610.0 (C=N), 1632.4 (C=O)	3.61, 3.79, 3.81, 3.90 (all s, 3 H each, OCH_3); 6.63 (d, 1 H, 2-Het, *J* = 2.6); 6.69—7.39 (m, 10 H, CH_{Ar}); 7.77 (d, 1 H, NH, *J* = 2.5); 8.77 (s, 1 H, N=CH)
22e	85	192—193	77.76 77.72	5.93 5.95	11.75 11.82	$C_{23}H_{21}N_3O$	3318.6 (N—H), 1608.4 (C=N), 1629.4 (C=O), 2919.4 (CH_3), 1505.0 (C_{Ar}=C)	2.20, 2.32 (both s, 3 H each, CH_3); 6.49 (d, 1 H, 2-Het, *J* = 2.5); 6.72 (t, 1 H, 6-Het, *J* = 7.0); 6.78 (d, 1 H, 8-Het, *J* = 8.5); 7.13—7.32 (m, 7 H, CH_{Ar}); 7.61—7.71 (m, 4 H, CH_{Ar}); 7.82 (d, 1 H, NH, *J* = 2.3); 8.88 (s, 1 H, N=CH)
22f	83	229—230	66.42 66.50	4.16 4.12	10.07 10.12	$C_{23}H_{17}N_3O_5$	914.1—930.7 (C—O—C, benzodioxole), 1500.9 (C=O), 1350.4 (C—N), 1609.6 (C_{Ar}=C), 1655.4 (C=N), 3296.6 (N—H)	5.96 (d, 2 H, OCH_2O, *J* = 1.4); 6.08 (d, 2 H, OCH_2O, *J* = 2.3); 6.33 (d, 1 H, 2-Het, *J* = 2.6); 6.69—6.88 (m, 4 H, CH_{Ar}); 6.94 (d, 1 H, CH_{Ar}, *J* = 1.1); 6.98 (d, 1 H, CH_{Ar}, *J* = 8.0); 7.17 (dd, 1 H, CH_{Ar}, *J* = 8.0, *J* = 1.3); 7.25 (s, 1 H, CH_{Ar}); 7.30 (t, 1 H, 7-Het, *J* = 7.7); 7.70 (d, 1 H, 5-Het, *J* = 6.9); 7.75 (d, 1 H, NH, *J* = 2.5); 8.78 (s, 1 H, N=CH)

disease.[22] This disease is difficult to treat due to the inaccessibility of neurons protected by the blood-brain barrier. Low-molecular-weight compounds have a chance to overcome the barrier, arrest the consequences of insufficient NPC1 protein activity, and to cease the cell death. Quinazolinone **11k** also forms different versions of the mRNA splicing of the *SMN2* gene. The *SMN2* gene encodes the protein significant for the stability of motor neurons. Abnormalities in the splicing of *SMN2* mRNA results in the nonfunctional protein synthesis.[23] As a result, the muscular atrophy progresses, which terminates by a fatal event for the patient. The correction of splicing processes can restore the normal functions of motor neurons. However, quinazolinone **11k** can have neurotoxicity due to inhibition of neuropeptide Y2.

Compound **11k** can facilitate the course of bloody flux,[24] since it inactivates Shiga toxins, which are produced by the *Shigella dysenteriae* pathogen.

Compound **11r** (CID 3712338) inhibits the NF-κB protein and thereon dependent signaling pathway. Moreover, it can blocks the CACNA1G calcium channel and increase the mitochondrial membrane permeability by activating *ClpP* and thereby facilitating initiation of the internal apoptosis pathway. The substance with such characteristics can have potent anticancer effect. At the same time, quinazolinone **11r** is the GRP7 neuropeptide recep-

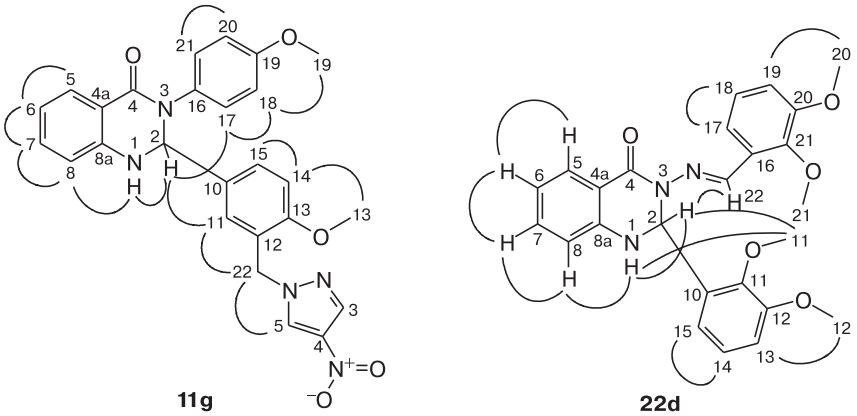


Fig. 1. NOESY correlation for quinazolinones **11g** and **22d**.

tor agonist and can have unpredictable effect on the nervous system of a patient.

The 6a*S*-enantiomer of derivative **18a** (CID 919001) blocks the TDP1 and ELG1 protein, which increases the genome instability in a tumor cell and can result in its death due to fatal abnormality in the gene transcription. In addition, tetracycle **18a** can decrease the intensity of tumor cell proliferation by suppression of the ATG4B protease function.

The racemic mixture of the tetracyclic compound **18a** (CID 3674352) is toxic for cardiomyocytes.

Compound **18a** decomposes the TDP-43 protein. It is known that this protein forms aggregations in the neuron cytoplasm. This is one of the reasons for the development of amyotrophic lateral sclerosis, incurable neurodegenerative disease.[25] The elimination of its aggregations can retard neurodegenerative processess and improve the status of the patient.

Thus, quinazolinones **11k**,**r** and **18a** exhibit anticancer activity by the mechanism of inhibition of DNA repair systems and proliferative activity. Compounds **11k** and **18a** can be useful in the therapy of neurodegenerative diseases. Compound **11k** was found to have a potential for the treatment of dysentery. However, to confirm the therapeutic activity and safety for healthy tissues, the above-described compounds must be subjected to comprehensive clinical trials.

Thus, the studies performed allowed us to synthesize a series of 1,2-dihydro-4(3*H*)-quinazolinone derivatives and the regularities found favored their tailor-made synthesis. The heterocorrelation ^{2}D NMR experiments allowed determining the structures of quinazolinones obtained.

According to the data from the bioactivity studies, the quinazolinone derivatives can have effective action on many molecular targets within cells. Based on the quinazolinone derivatives, one can design new anticancer and antiparasitic drugs, as well as can use them in the therapy of neurodegenerative diseases.

Experimental

The course of reactions and the purity of quinazolinones obtained were controlled by TLC on Silufol UV-254 plates using chloroform—methanol (8 : 2) as the eluent; the chromatograms were developed under an UV lamp and in iodine vapors. ^{1}H NMR spectra were recorded on a Bruker AVANCE III NanoBay Fourier-transform NMR spectrometer equipped with a superconducting magnet at a working frequency of 300 MHz in the mode of deuterium stabilization (thermal stabilization at 25 °C) using Me_4Si as the internal standard. Elemental analysis was performed on a Eurovector EuroEA 3000 CHNS analyzer. Melting points were measured on a standard melting point apparatus (PTP No. 26649) with certified thermometers. The ratio of enantiomers was determined by HPLC on an YMC CHIRAL NEA (R) chiral column (250×4.6 mm, 5 μm) using an UV detector at a wavelength of 220 nm.

Solvents and reagents (ACROS) were used as received. New aldehydes in required amounts were synthesized according to the earlier described procedures.[13]

Synthesis of anthranilic acid amides 7a—h (general procedure). To a solution of amine (0.05 mol) in pyridine (20 mL) cooled to 0—5 °C, a solution of phosphorus trichloride (0.01 mol) was added dropwise with stirring. After keeping for 0.5 h under these conditions, anthranilic acid (0.2 mol) was added and the mixture was heated on a water bath for 3—4 h with stirring. The reaction mixture was cooled to room temperature and, after standing, decanted from the precipitate of polyphosphorous acid. The solvent was removed *in vacuo*, the residue was treated with a mixture of ethyl acetate and diluted with hydrochloric acid (1 : 10). The organic layer was separated, washed with a solution of sodium bicarbonate, dried with sodium sulfate, and concentrated *in vacuo*. The precipitate was recrystallized from ethanol, the crystals formed were separated, and dried in air. The yields and physicochemical characteristics of amides **7a—h** are given in Table 1.

Synthesis of quinazolinones (general procedure). To a solution of amino amide (0.005 mol) in a xylene—acetic acid (1 : 1) mixture (10 mL), 0.005 mol of the corresponding aldehyde (0.01 mol for the synthesis of compound **22**) was added and the mixture was refluxed for 3—5 h (TLC control by aldehyde). After keeping under these conditions, the solvent was removed *in vacuo*, 2% hydrochloric acid was added to the residue, and the precipitate that formed was filtered off. The filter precipitate was washed with 5% soda solution and water and, if necessary, recrystallized from aqueous ethanol. The yields and physicochemical characteristics of 2-aryl quinazolinones **11a—y**, **12a—l**, **13a,b**, **16**, **18a**,**b**, and **22a—f** are given in Tables 2 and 3.

2-{4-Methoxy-3-[(4-nitro-1*H*-pyrazol-1-yl)methyl]phenyl}-3-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (11g). HPLC conditions: A) H_2O, 0.01% TFA; B) MeCN, 0.01% TFA,

45%; the flow rate was 1 mL min^{-1}, $t_R(1)$ = 19.55 min (56%); $t_R(2)$ = 21.41 min (43%). ^{13}C NMR (DMSO-d_6), δ: 51.09 (C(22)); 55.16 (C(20) (OMe)); 55.68 (C(14) (OMe)); 72.73 (C(2)); 110.72 (C(14)); 113.73 (C(20), C(18)); 114.54 (C(8)); 115.16 (C(4a)); 117.32 (C(6)); 123.48 (C(12)); 127.11 (C(11)); 127.77 (C(5)); 128.15 (C(15)); 128.25 (C(17), C(21)); 130.68 (C(5) (Pyr)); 132.83 (C(10)); 133.41 (C(16)); 133.48 (C(7)); 134.92 (C(4) (Pyr)); 135.80 (C(3) (Pyr)); 146.62 (C(8a)); 156.48 (C(13)); 157.29 (C(19)); 162.18 (C=O).

2-(4-Chlorophenyl)-3-(2-diethylaminoethyl)-2,3-dihydroquinazolin-4(1*H*)-one (12j). ^{13}C NMR (DMSO-d_6), δ: 12.02 ($CH_2\underline{C}H_3$); 42.89 (α-CH_2); 46.84 ($\underline{C}H_2CH_3$); 50.30 (β-CH_2); 70.06 (C(2)); 114.19 (C(8)); 114.76 (C(4a)); 117.18 (C(6)); 127.37 (C(5)); 128.14 (*m*-C_{Ar}); 128.52 (*o*-C_{Ar}); 132.98 (quat. $C_{Ar}Cl$); 133.21 (C(7)); 140.15 (quat. C_{Ar}); 146.12 (C(8a)); 162.11 (C=O).

3-(2-Diethylaminoethyl)-2-(3-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (12k). ^{13}C NMR (DMSO-d_6), δ: 12.01 ($CH_2\underline{C}H_3$); 43.02 (α-CH_2); 46.83 ($\underline{C}H_2CH_3$); 50.31 (β-CH_2); 70.05 (C(2)); 113.31, 113.02 ($C(2)_{Ar'}$); 114.21 (C(8)); 114.83 ($C(4)_{Ar'}$); 115.06 (C(4a)); 115.34 ($C(4)_{Ar'}$); 117.25 (C(6)); 122.21, 122.17 ($C(6)_{Ar'}$); 127.36 (C(5)); 130.66, 130.56 ($C(5)_{Ar'}$); 133.23 (C(7)); 144.22, 144.15 ($C(1)_{Ar'}$); 146.13 (C(8a)); 160.50 ($C(3)_{Ar'}$); 162.11 (C=O); 163.74 ($C(3)_{Ar'}$).

(*E*)-3-(2,3-Dimethoxybenzylidineamino)-2-(2,3-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (22d). HPLC conditions: A) H_2O, 0.01% TFA; B) MeCN, 0.01% TFA, 50%; the flow rate was 1 mL min^{-1}, $t_R(1)$ = 12.33 min (56%); $t_R(2)$ = = 13.36 min (43%). ^{13}C NMR (DMSO-d_6), δ: 55.77 (C(20) (OMe)); 55.80 (C(12) (OMe)); 60.52 (C(21) (OMe)); 61.06 (C(11) (OMe)); 67.58 (C(2)); 113.29 (C(13)); 113.97 (C(4a)); 114.57 (C(19)); 114.74 (C(8)); 116.88 (C(17)); 117.58 (C(6)); 117.78 (C(15)); 123.95 (C(14)); 124.31 (C(18)); 127.80 (C(16)); 128.02 (C(5)); 132.79 (C(10)); 133.99 (C(7)); 145.82 (C(8a)); 145.90 (C(11)); 145.95 (C(22)); 148.29 (C(21)); 152.55 (C(12)); 152.63 (C(20)); 160.75 (C(4)).

Biological experiments. The data were obtained using the HTS method and loaded to the Pubchem database.[19] The HTS method is robotized: all experiments are automated. The obtained preliminary data are generated by the program algorithm carrying out HTS and the most significant data are loaded to open access. If compounds have no effect on cell lines, these data are not loaded to open access. The "crude" research data include cell lines for which the effects exerted by new compounds were detected. The signaling pathways of cells on which these compounds have effect are described. The results allows making decision on which signaling pathways in tumor cells are disturbed. In our study, the resulting data are interpreted in order to determine the mechanism of biological actions of new compounds, including anticancer and antiparasitic ones.

The authors are grateful to M. A. Yurovskaya for invaluable help and support in the discussion and preparation of this work, as well as to the researchers of the Analytical Test Center of the Federal State Unitary Enterprise "IREA" for their help in the structural determination of synthesized compounds.

This work was financially supported in part by the Ministry of Education and Science of the Russian Federation (Grant Agreement No. 14.576.21.0044 dated on August 5, 2014, the Federal Target Program "Research and Development in High-Priority Development Trends of the Scientific and Technological Complex of Russia for 2014—2020", unique identifier RFMEFI57614X0044).

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Received March 1, 2016;
in revised form February 16, 2017