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Small synthetic molecules with antiglycation activity. Structure – activity relationship

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The accumulation of advanced glycation end products (AGEs) is currently considered as one of the key factors in aging processes, the pathogenesis of late complications of diabetes mellitus, cancer and neurodegenerative diseases. This review is devoted to small synthetic molecules with antiglycation activity, *i.e.*, compounds with the ability to inhibit AGE formation. Molecules with antiglycation activity in the low micromolar range (<10 μM), primarily fused heterocyclic systems containing oxygen or nitrogen as heteroatoms and (thio)ureas, have been discovered to date. The known scaffolds with antiglycation activity are analyzed, structural modifications to enhance antiglycation abilities are highlighted and the structure – activity relationships are discussed.
The bibliography includes 125 references.

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1. Introduction

Diabetes is a group of endocrine disorders associated with the chronic disturbance of glucose metabolism and, in the absence of therapy, leading to the development of various complications, which significantly impair the health-related quality of life and work ability. In 2019, diabetes was the seventh leading cause of death with an estimated 4.2 million diabetes-associated deaths worldwide.[1] According to the World Health Organization, about 8.8% of adults (463 million people) are living with diabetes all over the world,[1] type 2 diabetes mellitus (T2DM) accounting for about 90% of all cases of diabetes. As opposed to T1DM, which is characterized by the impairment of pancreatic insulin secretion, T2DM is caused by insulin resistance, which results in a decrease in response to insulin in tissues, thereby impairing glucose metabolism and, correspondingly, leading to consistently high blood glucose levels referred to as hyperglycemia.[2] From the chemical point of view, glucose is a quite reactive molecule, being involved in the glycation of proteins, lipids and nucleic acids to form advanced glycation end products (AGEs).[3] The classical example of AGEs is glycated haemoglobin (HbA1c), which is one of key markers for the diagnosis and treatment of diabetes.[4] Despite a wide range of available blood sugar-lowering agents used in the therapy of T2DM, the target levels of HbA1c are reached by less than 50% of patients with T2DM.[5] Therefore, the design of new drugs for the therapy of T2DM, which have other mechanisms of action, is a challenge.

It is worth noting that the key role of AGEs in aging processes and pathogenesis not only of diabetes [6] but also of cancer [7] and neurodegenerative diseases [8] has been discussed in a growing number of recent studies. These observations are supported by the mechanism of AGE formation, which demonstrates the potential of the nonenzymatic reaction of

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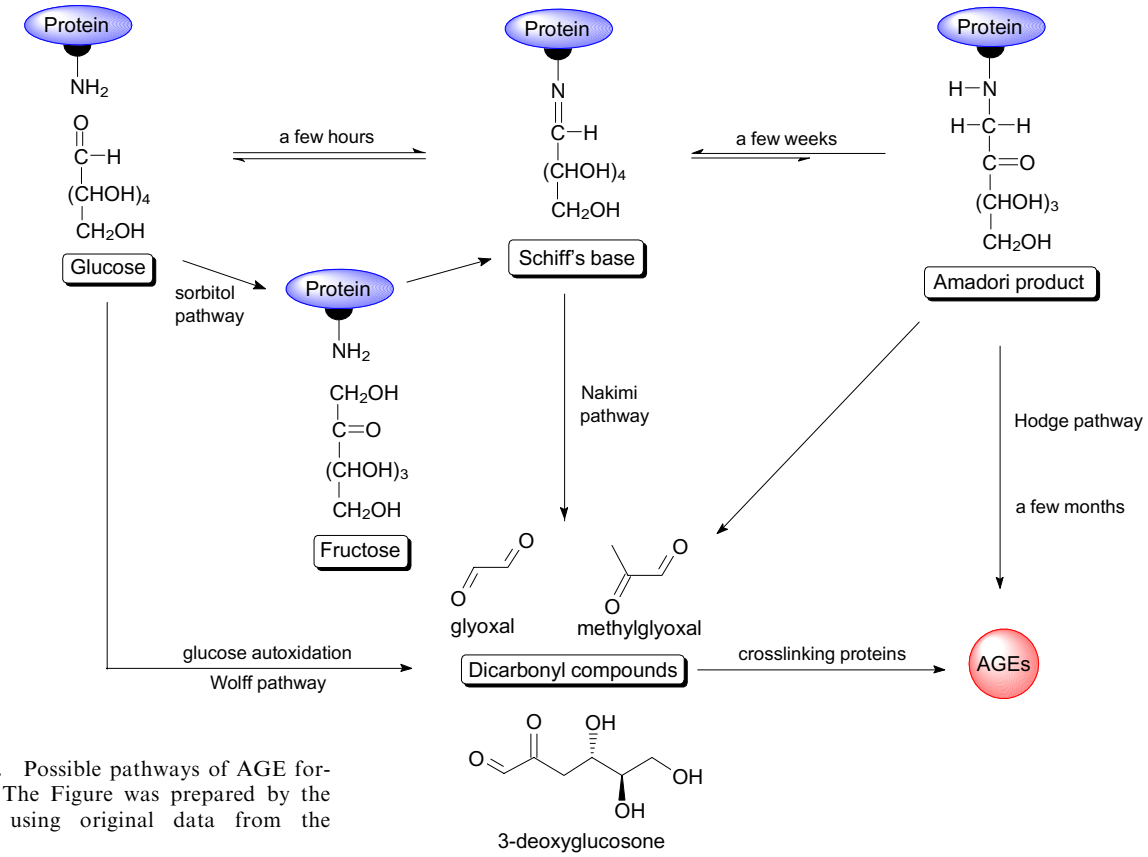


Figure 1. Possible pathways of AGE formation. The Figure was prepared by the authors using original data from the study.[9]

sugars (glucose, galactose, fructose) with any tissue of the body containing free amino groups (Fig. 1).[9]

It is emphasized that the major reactions producing AGEs involve cascades exclusively of nonenzymatic reactions of different degrees of reversibility.[10] However, for the maintenance of the integrity of the body, substrates for AGE formation can be generated through metabolic pathways involving, in particular, enzymes. This is attributed to the deep relationship between metabolic pathways in the body. One of carbonyl compounds serving as precursors of AGEs is methylglyoxal (MGO), the metabolism of which is described in detail in the study.[11] The levels of MGO in the plasma and tissues depend on the balance between its anabolism and catabolism. The glycolysis (regulated enzymatically) is the main source of MGO in mammals. Besides, aminoacetone or acetone, the formation of which is catalyzed by semicarbazide-sensitive amine oxidase (SSAO) or acetone monooxygenase (AMO), respectively, also serve as sources of MGO. The enzyme SSAO is present at high levels in the human plasma and its activity correlates with the development of pathologies dependent on the advancement of glycation and AGE formation.[11] Thus, the activation of SSAO accelerates glycation.[12] However, it is worth noting that the concentration of enzymatically produced carbonyl substrates for glycation is very low (in particular, 125 μM day^{-1} for MGO, M is molar concentration)[11] compared to the glucose concentration (the normal glucose level in humans is 3300–5500 μM). This is why the nonenzymatic conversion of glucose (and other monosaccharides) in glycation reactions is the major source of AGEs.[10]

Advanced glycation end products have dual pathology. First, the direct covalent modification of the protein can impair its proteolytic degradation and interaction with other macromolecules and also affect the biomechanical characteristics of tissues.[13] Second, there is a receptor-mediated pathway associated with the induction and activation of receptors for advanced glycation end products (RAGEs), triggering anti-inflammatory pathways and atherogenic effects.[14] Since RAGEs are constitutively highly expressed in the lung, there is evidence for the relationship between this type of receptors and the development of life-threatening complications of COVID-19, such as cytokine storm.[15]

It should be emphasized that AGEs are produced in healthy humans as well (both endogenously and exogenously depending on nutrition[16]). However, at a low concentration of these AGEs, the mechanisms of their cleavage and excretion from the body, primarily by kidneys, are also efficient.[17] In the case of diabetic hyperglycemia, the rate of protein glycation significantly increases, the concentration of AGEs becomes higher and their diversity becomes greater, giving rise to complications of T2DM and causing an increased risk of developing other diseases associated with the effect of AGEs.

Currently, the main approaches to the protection against adverse effects of AGEs involve the prevention of their formation (antiglycation activity), the cleavage of cross-linkages related to AGE production and the neutralizing effects (*e.g.*, through the inhibition of RAGE). The inhibition of AGE formation is the most well-studied process widely represented in the literature. Since the mechanism of AGE formation involves numerous steps (see Fig. 1), the approaches to the inhibition of this processes are based on different mechanisms. Thus, aminoguanidine and related compounds are linked to α-dicarbonyl compounds *via* direct covalent binding, thereby

preventing their interaction with proteins and AGE formation.[18] It is worth noting that aminoguanidine was considered as a drug candidate with the mechanism of antiglycation, but it was withdrawn from phase III clinical trials because of adverse side effects.[19] It was demonstrated that many natural antioxidants have antiglycation effect due to the binding of free radicals, which catalyze early stages of formation of substrates in the route to AGEs, primarily the glucose autoxidation and Schiff base oxidation.[9] Besides, it is assumed that the activation of RAGE can lead to an increase in the rate of AGE formation,[9] whereas the inhibition of this type of receptors, on the contrary, reduces the AGE level.[20] It is known that transition metal cations, primarily Fe^{2+}, Fe^{3+}, Cu^{+} and Cu^{2+}, play a significant role as catalysts for the generation of highly reactive carbonyl compounds and free radicals, resulting in AGE formation. Correspondingly, compounds capable of chelating these cations can inhibit the synthesis of AGEs.[21] A number of studies demonstrated that the enzymatic pathway of AGE formation can also be inhibited. In particular, metformin enhances the activity of glyoxalase I, which catalyzes the metabolism of the major portion of MGO as a precursor of AGEs; however, it was mentioned that the antidiabetic effect of metformin is also related to the decrease in the overall blood glucose level and the covalent binding of MGO.[22, 23]

It is worth noting that natural substances with antiglycation activity, primarily various plant extracts and compounds that are present in foods, have received extensive attention in the literature.[24–26] Brief chapters on the antiglycation activity of synthetic molecules are included in reviews devoted to biological activity of particular classes of compounds.[27, 28] There are a number of reviews addressing the mechanism of glycation[29–31] and the pathogenesis of glycation-associated complications,[32] which consider the accumulation of AGEs in the body and possible ways to combat this problem, in particular, using compounds with antiglycation activity. The review[29] focuses on the possible effects on enzyme systems to defend against the accumulation of AGEs, while this pathway is considered as the minor source of AGE formation.[10] Only patent literature is discussed in the publication,[31] while a few most well-known compounds with antiglycation activity were mentioned in reviews.[30, 32] The whole palette of scaffolds with antiglycation activity, which were reported in the literature, is considered in none of the publications. Besides, the structure–activity relationship analysis, which is a key issue in the design of new molecules with a strong antiglycation effect, is lacking.

Therefore, the goals of this review are to consider small synthetic molecules with antiglycation activity, survey the available scaffolds and construct structure—activity relationships in order to reveal the most promising classes of molecules and their representatives. Besides, the impetus for writing this review was the diversity of classes of molecules, which were examined for the ability to inhibit the formation of AGEs. This diversity, on the one hand, can be attributed to a complex mechanism of AGE formation and, on the other hand, is indicative of the absence of the general idea of structure—activity relationships.

Since compounds exhibiting antiglycation activity are structurally very diverse, their classification is a difficult and arbitrary task. Hence, we classified the compounds according to the chemical structure of the major scaffold, which remained unchanged when studying the antiglycation activity, while the structural optimization was performed to enhance this effect by varying the substituents on the scaffold. Therefore, the review includes the following sections: (thio)ureas, hydrazines and their imine derivatives, phenols and quinones, isatin and benzimidazole derivatives, benzopyranones and their derivatives. Besides, some molecules do not fall into this classification and are considered as individual scaffolds: carbonyl compounds, non-fused and benzannulated heterocyclic systems and miscellaneous fused heterocyclic systems.

2. Scaffolds with antiglycation activity

2.1. (Thio)ureas

We start the consideration of compounds exhibiting antiglycation activity with (thio)ureas because these molecules are structural analogues of aminoguanidine (Fig. 2), which was considered as one of the first promising drug candidates with the mechanism of antiglycation for the treatment of diabetes mellitus-associated nephropathy.[23]

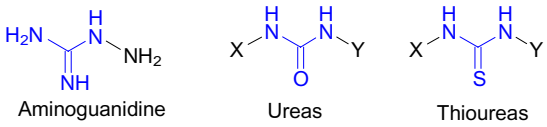


Figure 2. Structures of aminoguanidine and (thio)ureas.

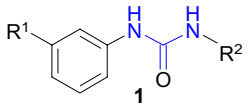
Choudhary and co-workers[33] evaluated the antiglycation activity of unsymmetrical ureas **1** and found several compounds with a half-maximal inhibitory concentration in the low micromolar range (Table 1). Ureas containing a bromine atom (**1b**, IC_{50} = 4.26 μM) or a methoxy group (**1c**, IC_{50} = 5.8 μM) in the *meta* position of one phenyl substituent R proved to be the most active. Meanwhile, 3,4-dimethyl derivative **1a** exhibited high antiglycation activity (IC_{50} = 9 μM), whereas in all other cases, the related dimethyl-containing structures have no effect on the AGE formation.

The evaluation of the antiglycation activity of nitro-containing phenylureas **2** demonstrated that the nitro group, particularly in the *ortho* or *meta* position, causes a significant decrease in the ability of this series of compounds to inhibit AGE formation.[34] More than a half of 21 tested compounds showed the statistically significant activity with the half-maximal inhibitory concentration was in the high micromolar range (Table 2).

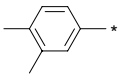
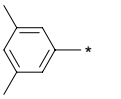
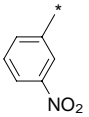
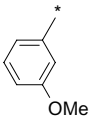
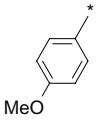
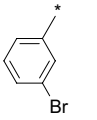
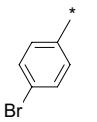
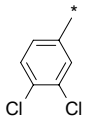
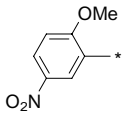
Vardhan *et al.*[35] studied piperazine amide derivatives of glycine **3** and proline **4** modified with urea and thiourea moieties. The authors mentioned that the general structure—activity relationships were observed in the whole series of compounds **3** and **4** regardless of the nature of the heteroatom of the urea moiety and the type of amino acid (Table 3). Thus, the presence of halogen atoms in the phenyl substituent enhances antiglycation activity, whereas the introduction of a hydroxymethyl substituent, on the contrary, leads to a decrease in the ability to inhibit the AGE formation. It was demonstrated that the presence of a halogen atom in the *meta* position of the phenyl ring is favourable for activity (lead compound **4a**, $IC_{50} = 1.52 \pm 0.02$ μM).

In the subsequent study, Suyoga Vardhan *et al.*[36] examined the effect of the replacement of glycine and proline

Table 1. Antiglycation activity of compounds **1**.[33]



1

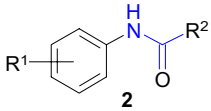
R^2	$IC_{50} \pm SEM$, μM	
	R^1 = H	R^1 = Cl
	9 ± 0.35 (**1a**)	ND
	ND	905.9 ± 3.8
	ND	7.02 ± 0.31
	7.27 ± 0.36	ND
	229 ± 11.8	5.8 ± 0.08 (**1b**)
	8.4 ± 0.15	7.14 ± 0.84
	120.4 ± 14.6	6.6 ± 0.26
	4.26 ± 0.25 (**1c**)	8.16 ± 1.04
	6.1 ± 0.13	6.4 ± 0.02
	838.3 ± 3.14	15.22 ± 6.7
	162.5 ± 16.8	407.6 ± 1.7

Note. Here and in other Tables, ND means not determined.

substituents by other amino acid moieties on the antiglycation activity of the resulting compounds and revealed the following structure – activity relationships (Table 4):

1) there is no significant difference in the antiglycation activity between ureas and thioureas;

Table 2. Antiglycation activity of compounds **2**.[34]



2

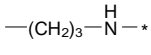
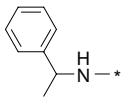
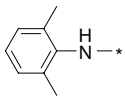
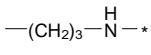
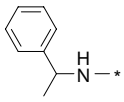
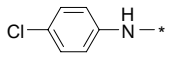
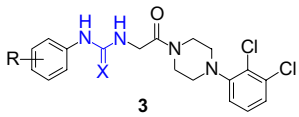
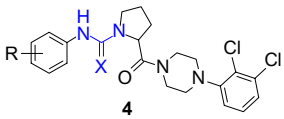
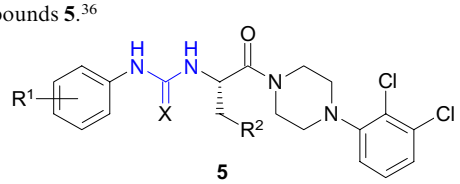
R^1	R^2	$IC_{50} \pm SEM$, μM
2-NO_2		624.84 ± 11.43
2-NO_2		723.15 ± 5.31
2-NO_2		408.44 ± 27.05
3-NO_2		985.56 ± 4.89
3-NO_2		903.49 ± 6.73
4-NO_2		147.55 ± 2.07
4-NO_2		281.36 ± 6.07
4-NO_2		909.71 ± 2.63
4-NO_2		910.07 ± 14.31

Table 3. Antiglycation activity of compounds **3** and **4**.[35]

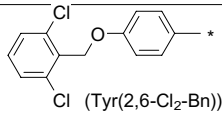
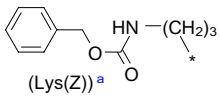
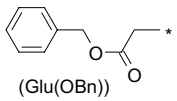
R	$IC_{50} \pm SEM$ μM			
	 **3**		 **4**	
	X = O	X = S	X = O	X = S
H	390.85 ± 0.32	360.98 ± 0.29	240.36 ± 0.25	318.9 ± 0.37
2-F	60.02 ± 0.26	135.20 ± 0.62	49.90 ± 0.03	91.20 ± 0.23
3-F	3.90 ± 0.08	ND	2.32 ± 0.03	5.33 ± 0.04
4-F	70.08 ± 0.06	30.20 ± 0.07	4.02 ± 0.07	4.85 ± 0.10
3-Cl	2.60 ± 0.04	6.20 ± 0.09	1.52 ± 0.02 (**4a**)	4.20 ± 0.08
4-Cl	ND	5.53 ± 0.06	ND	ND
2-Br	ND	3.82 ± 0.05	ND	ND
3-Br	2.20 ± 0.11	1.95 ± 0.02	3.42 ± 0.15	4.92 ± 0.10
4-Br	4.81 ± 0.10	ND	6.05 ± 0.05	4.62 ± 0.08
2-OMe	165.70 ± 0.62	NA	113.2 ± 0.24	37.42 ± 0.87
3-OMe	125.01 ± 0.07	45.13 ± 0.24	63.00 ± 0.32	128.2 ± 0.62
4-OMe	85.03 ± 0.78	40.20 ± 0.06	68.20 ± 0.76	110.08 ± 0.85

Note. Here and in other Tables, NA means not active.

Table 4. Antiglycation activity of compounds **5**.[36]



5

R^1	X	$IC_{50} \pm SEM$, μM						
		R^2						
		Ph (Phe)	C_6H_4-4-OH (Tyr)	 (Tyr(2,6-Cl_2-Bn))	$(CH_2)_3NH_2$ (Lys)	 (Lys(Z))[a]	CH_2CO_2H (Glu)	 (Glu(OBn))
H	O	176.2 ± 1.65	125.0 ± 2.08	131.19 ± 3.23	215.18 ± 5.05	265.15 ± 4.25	92.34 ± 1.32	100.0 ± 3.05
3-Br	O	5.28 ± 0.83	1.60 ± 1.00	1.80 ± 0.96	2.08 ± 1.05	2.20 ± 1.09	1.18 ± 0.62	1.35 ± 0.95
4-Br	O	4.12 ± 1.25	4.22 ± 2.12	4.72 ± 2.25	3.42 ± 1.39	4.18 ± 2.25	2.80 ± 0.99	3.85 ± 2.12
3-F	O	1.89 ± 0.90	1.59 ± 0.52	2.00 ± 1.09	3.59 ± 2.13	4.10 ± 2.38	2.72 ± 1.18	3.85 ± 1.18
4-F	O	1.75 ± 0.71	2.48 ± 1.05	2.60 ± 1.03	2.75 ± 1.05	3.09 ± 1.08	1.75 ± 0.90	1.90 ± 0.63
3-Cl	O	1.15 ± 0.85 (**5a**)	1.40 ± 0.52	1.82 ± 0.95	1.89 ± 0.80	2.75 ± 0.82	1.67 ± 0.68	2.29 ± 1.32
H	S	145.0 ± 1.21	175.98 ± 1.92	180.24 ± 4.08	224.56 ± 4.52	250.10 ± 5.13	54.21 ± 2.65	60.25 ± 2.95
2-Br	S	2.00 ± 0.9	1.79 ± 0.95	1.96 ± 0.79	1.62 ± 0.91	2.00 ± 1.19	3.16 ± 1.15	4.09 ± 2.98
3-Br	S	4.58 ± 1.22	3.42 ± 1.02	4.40 ± 1.12	3.02 ± 1.12	3.12 ± 1.95	1.45 ± 0.74	1.85 ± 0.86
4-F	S	5.00 ± 1.65	2.72 ± 1.49	3.10 ± 1.24	3.31 ± 1.23	3.89 ± 2.25	1.71 ± 0.79	1.96 ± 0.90
3-Cl	S	4.00 ± 2.15	1.47 ± 0.98	1.92 ± 0.83	3.02 ± 1.09	3.79 ± 1.25	3.94 ± 1.09	4.10 ± 1.11
4-Cl	S	4.45 ± 2.20	3.59 ± 2.07	4.59 ± 2.17	3.19 ± 1.10	4.00 ± 2.04	3.57 ± 1.18	3.90 ± 1.27

Note. Bn = CH_2Ph. [a] Z = C(O)OBn.

2) a halogen atom in the phenyl ring bound to the (thio)urea moiety plays a significant role in the activity;

3) the type of the halogen atom (fluorine, chlorine, bromine) has an insignificant effect on the IC_{50} value;

4) the activity depends on the type of the amino acid moiety in the molecule and decreases in the series Glu > > Glu(OBn) > Tyr > Tyr(2,6-Cl_2-Bn) > Lys > Lys(Z) > Phe.

More recently, this research group studied benzisoxazoles covalently linked to phenyl(thio)ureas through various amino acid moieties.[37] Based on the structure—antiglycation activity relationship analysis of this series of compounds (Table 5), the following conclusions were drawn:

1) thioureas are in general more active than the oxygen-containing analogues;

2) in the case of bromo derivatives, the activity decreases in the series *para* > *ortho* > *meta*;

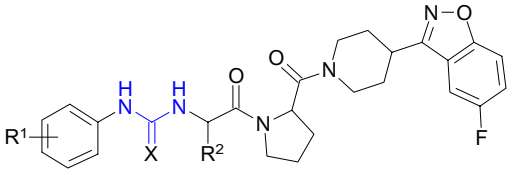
3) in the case of methoxy derivatives, the *ortho* derivatives are more active than the *meta*-substituted compounds;

4) the activity depends on the nature of the amino acid moiety in the molecule and decreases in the series Tyr(2,6-Cl_2-Bn) > Phe > Val > Lys(Z).

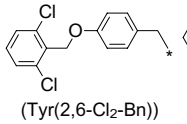
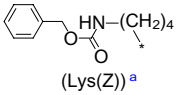
The binding of phenyl(thio)ureas to benzisoxazole through a glycine or proline moiety gives rise to even more active compounds **7** and **8** (Table 6). In this case, the above relationship is retained. Thus, thioureas are in general more active than the oxygen-containing analogues, and the bromine atom or the methoxy groups are the most preferable substituents on the phenyl moiety because the presence of a fluorine or chlorine atom leads to a significant decrease in the antiglycation activity.[38]

The replacement of amino acid moieties by other linkers confirmed the previously revealed structure–activity relationships (Table 7).[39] In the series of compounds **3**–**9**, thiourea **9a** proved to be the lead compound with respect to the antiglycation activity, with the half-maximal inhibitory concentration IC_{50} = 1.9 ± 0.2 μM.

Table 5. Antiglycation activity of compounds **6**.[37]



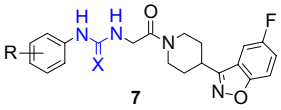
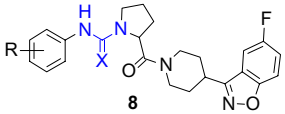
6

R^1	X	$IC_{50} \pm SEM$, μM			
		R^2			
		Pr^i (Val)	Bn (Phe)	 (Tyr(2,6-Cl_2-Bn))	 (Lys(Z))[a]
3-OMe	O	55.0 ± 0.8	53.0 ± 0.3	47.5 ± 0.5	68.0 ± 0.8
4-OMe	O	54.0 ± 0.3	32.0 ± 0.4	28.0 ± 0.3	39.0 ± 0.3
3-Br	O	77.0 ± 0.2	42.0 ± 0.8	57.0 ± 0.3	93.0 ± 0.3
4-Br	O	65.0 ± 0.2	51.0 ± 0.6	43.0 ± 0.4	54.0 ± 0.4
3-OMe	S	39.0 ± 0.2	37.0 ± 0.4	31.5 ± 0.4	50.0 ± 0.7
4-OMe	S	13.1 ± 0.5	12.4 ± 0.3	4.3 ± 0.5	18.4 ± 0.4
2-Br	S	31.0 ± 0.1	19.5 ± 0.2	17.1 ± 0.7	37.5 ± 0.4
3-Br	S	55.0 ± 0.6	36.0 ± 0.3	40.0 ± 0.5	87.0 ± 0.2

[a] Z = C(O)OBn.

The evaluation of the antiglycation activity of urea precursors **9**, such as *tert*-butyl carbamates **10**, demonstrated that the latter compounds exhibit much lower antiglycation activity (IC_{50} = 365.8–425.4 μM). Conse-

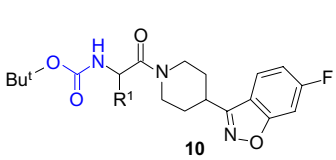
Table 6. Antiglycation activity of compounds **7** and **8**.[38]

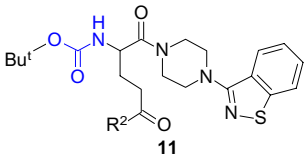
R	IC$_{50}$ ± SEM, μM			
	 **7**		 **8**	
	X = O	X = S	X = O	X = S
H	390.4 ± 0.4	380.5 ± 0.8	340.1 ± 0.5	295.1 ± 0.3
2-OMe	20.2 ± 0.3	4.1 ± 0.6	30.6 ± 0.7	5.2 ± 0.4
3-OMe	21.1 ± 0.1	15.3 ± 0.8	33.4 ± 0.2	20.5 ± 0.1
3-OMe	19.5 ± 0.4	3.6 ± 0.3	22.1 ± 0.7	3.9 ± 0.4
2-F	55.5 ± 0.7	9.1 ± 0.5	54.8 ± 0.9	7.8 ± 0.8
3-F	100.2 ± 0.6	ND	116.7 ± 0.1	ND
4-F	75.8 ± 0.2	70.3 ± 0.7	76.1 ± 0.4	70.9 ± 0.6
3-Cl	143.5 ± 0.5	NA	145.4 ± 0.7	125.7 ± 0.8
4-Cl	83.9 ± 0.9	NA	60.3 ± 0.3	59.4 ± 0.8
3-Br	9.3 ± 0.4	4.9 ± 0.7	6.9 ± 0.4	4.7 ± 0.1
4-Br	8.5 ± 0.5	6.3 ± 0.8	6.8 ± 0.6	7.8 ± 0.2

quently, the phenyl(thio)urea moiety is essential for the inhibition of AGE formation. Similar relationships were observed also in the series of benzoisothiazoles. Thus, the corresponding *tert*-butyl carbamates **11** were found to be less active than (thio)urea derivatives **12** (Table 8).[40]

All compounds of series **12** proved to be active in the mid-micromolar range (IC$_{50}$ = 30–67 μM) (see Table 8), the thioureas exhibiting a somewhat stronger antiglycation effect compared to the oxygen-containing analogues. Besides, it was noted that the methoxy group in the phenyl ring facilitates a slight increase in the antiglycation activity, as opposed to the corresponding fluorine-substituted compounds.

Structures 10, 11


10


11

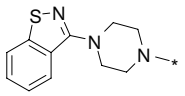
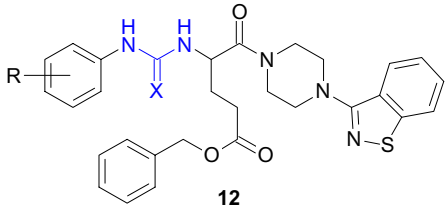
R^2	OH	OBn	
IC$_{50}$, μM	160 ± 0.8	95 ± 0.7	80 ± 0.2

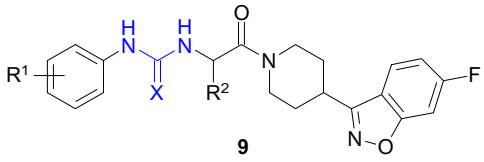
Table 8. Antiglycation activity of compounds **12**.[40]


12

R	IC$_{50}$ ± SEM, μM	
	X = O	X = S
2-F	56 ± 0.3	49 ± 0.2
3-F	67 ± 0.3	ND
4-F	45 ± 0.1	39 ± 0.3
2-OMe	33 ± 0.4	48 ± 0.3
3-OMe	52 ± 0.2	39 ± 0.2
4-OMe	43 ± 0.4	30 ± 0.2

The activity can be additionally enhanced by using the bis-benzoisothiazole scaffold. Lead compounds **13b** (IC$_{50}$ = 10 ± 0.1 μM) and **13a** (IC$_{50}$ = 11 ± 0.4 μM) were

Table 7. Antiglycation activity of compounds **9**.[39]


9

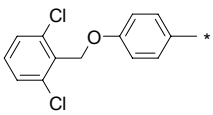
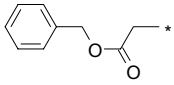
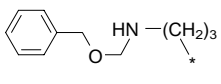
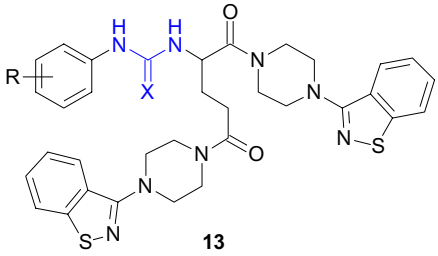
R^1	X	IC$_{50}$ ± SEM, μM			
		R^2			
		Bn			
H	O	75.6 ± 0.5	80.2 ± 0.2	64.1 ± 0.8	81.8 ± 0.8
3-Br	O	9.3 ± 0.5	8.8 ± 0.3	8.2 ± 0.6	9.1 ± 0.2
4-Br	O	9.2 ± 0.4	8.2 ± 0.2	8.0 ± 0.5	7.4 ± 0.8
H	S	70.3 ± 0.3	74.4 ± 0.3	55.2 ± 0.2	74.1 ± 0.7
2-OMe	S	3.6 ± 0.2	3.0 ± 0.3	2.9 ± 0.3	3.8 ± 0.3
3-OMe	S	4.8 ± 0.5	4.4 ± 0.4	4.8 ± 0.5	4.5 ± 0.4
4-OMe	S	3.0 ± 0.4	1.9 ± 0.2 (**9a**)	2.5 ± 0.3	3.0 ± 0.4
2-Br	S	6.4 ± 0.3	4.8 ± 0.7	5.2 ± 0.2	6.1 ± 0.3
3-Br	S	6.5 ± 0.2	6.5 ± 0.6	6.5 ± 0.2	7.0 ± 0.4
2-F	S	23 ± 0.6	15.4 ± 0.4	15.1 ± 0.5	20.6 ± 0.7

Table 9. Antiglycation activity of compounds **13**.[40]



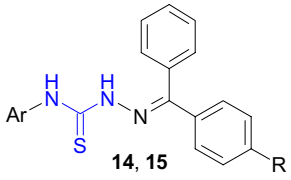
13

R	IC$_{50}$ ± SEM, μM	
	X = O	X = S
H	30 ± 0.6	25 ± 0.5
2-F	22 ± 0.4	21 ± 0.1
3-F	23 ± 0.3	ND
4-F	22 ± 0.1	21 ± 0.2
3-Cl	115 ± 0.9	95 ± 0.6
4-Cl	57 ± 0.1	48 ± 0.3
3-Br	145 ± 0.4	180 ± 0.9
4-Br	150 ± 0.5	135 ± 0.8
2-OMe	14 ± 0.5	11 ± 0.4 (**13a**)
3-OMe	22 ± 0.1	19 ± 0.2
4-OMe	12 ± 0.3	10 ± 0.1 (**13b**)

revealed among the corresponding derivatives. It was demonstrated that the replacement of the fluorine atom or the methoxy group by heavy chlorine or bromine atoms leads to a significant decrease in the antiglycation effect (Table 9).

Abbasi *et al.*[41] synthesized two series of triphenylthiosemicarbazones **14** and **15** and evaluated them for antiglycation activity. It was found that the presence of a hydroxyl group in the *para* positon of the benzophenone moiety plays a significant role in this type of activity because all compounds **14**, which do not contain this functional group, proved to be inactive. On the other hand, the activity of hydroxy derivatives **15** was also observed only in the high micromolar range (IC$_{50}$ = 118.15–488.54 μM).

Structures 14, 15



14, 15

R = H (**14**),
OH (**15**)

Based on the data on the ability of (thio)ureas to inhibit the formation of AGEs, it can be concluded that this scaffold holds promise because a large number of derivatives exhibit antiglycation activity in the low micromolar range (1–10 μM), up to IC$_{50}$ = 1–2 μM. The following structural features were found to influence the ability to inhibit AGE formation (Fig. 3):

— the oxygen or sulfur atom can serve as X; the difference in the activity of thioureas and ureas is generally small;

— the presence of an *ortho* or *para* substituent on the phenyl moiety R is the most favourable for activity; halogen atoms as substituents enhance the antiglycation activity, whereas methyl, methoxy and nitro groups generally lead to a decrease in this activity;

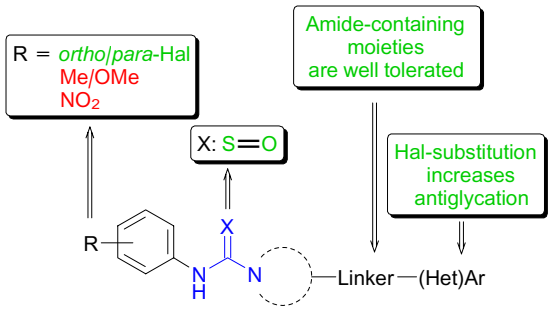


Figure 3. Structure–activity relationship for the (thio)urea scaffold.

— various moieties can serve as linkers, having no significant effect on the antiglycation activity; generally, these are piperazine-containing amide moieties;

— the (Het)Ar moiety can be varied in a rather wide range; the replacement of this moiety by a halogen atom is favourable for the enhancement of antiglycation activity;

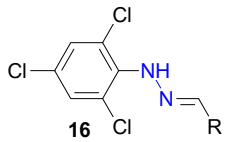
— the replacement of the (thio)urea scaffold by the carbamate moiety [R^{1}OC(O)NHR^2] leads to the loss of antiglycation activity.

2.2. Hydrazines and their imine derivatives

Compounds containing substituted hydrazines or their imine derivatives as the key moiety were investigated. Thus, 2,4,6-trichlorophenylhydrazones **16** bearing hydroxyl moieties in the phenyl substituent R were found to be able to inhibit AGE formation (Table 10).[42]

Another series of hydrazones, such as Schiff bases **17**, produced from benzophenone, and their antiglycation activity were described by Khan *et al.*[43] It was found that

Table 10. Antiglycation activity of compounds **16**.[42]



16

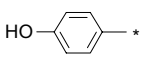
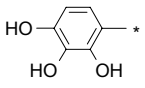
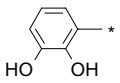
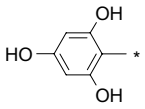
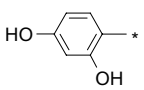
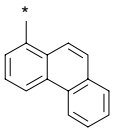
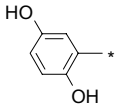
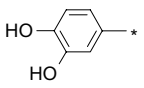
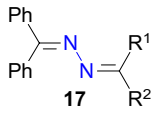
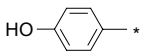
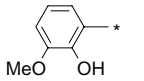
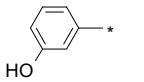
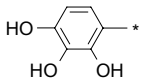
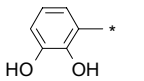
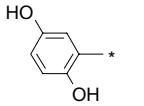
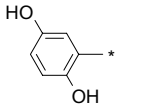
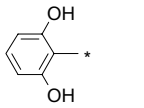
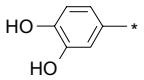
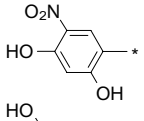
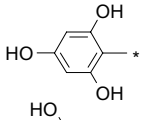
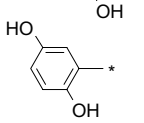
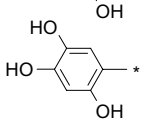
R	IC$_{50}$ ± SEM, μM	R	IC$_{50}$ ± SEM, μM
	276 ± 0.014		354 ± 0.008
	55.7 ± 0.00		175 ± 0.004
	178 ± 0.005		949 ± 0.019
	95 ± 0.004		NA
	27.2 ± 0.00		NA

Table 11. Antiglycation activity of compounds **17**.[43]



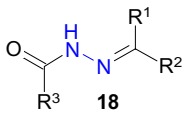
17

R^1	R^2	$IC_{50} \pm SEM$, μM	R^1	R^2	$IC_{50} \pm SEM$, μM
H		262 ± 0.013	H		305 ± 0.019
H		237 ± 0.021	H		174 ± 0.002
H		25.7 ± 0.003	Me		56.2 ± 0.023
H		66 ± 0.002	Me		57 ± 0.002
H		49.5 ± 0.001	Me		36.6 ± 0.004
H		146 ± 0.007	Et		67.9 ± 0.001
H		113 ± 0.005			

the enhancement of antiglycation activity is associated with the presence of a hydroxyl group on the phenyl substituent R^2, the highest activity being observed for polyphenols (Table 11).

The further evaluation of antiglycation activity of related Schiff bases **18** demonstrated that the replacement of the methylenediphenyl moiety (compounds **17**) by the acyl or formyl group causes a significant decrease in the ability to inhibit AGE formation.[44] Thus, most of structures **18** did not have an antiglycation effect, and the remaining compounds were characterized by the transition of the half-maximal inhibitory concentration from the mid- to high micromolar range (IC_{50} = 199.82 – 664.81 μM).

Structure 18



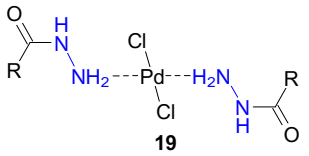
18

R^1, R^2 = (Het)Ar;
R^3 = H, Me

Mustafa and co-workers[45] demonstrated that *ortho*- or *meta*-substituted benzoyl hydrazides are more active than the corresponding *para*-substituted derivatives; however, the half-maximal inhibitory concentrations for all palladium complexes **19** were observed in the high micromolar range (IC_{50} = 385 – 714 μM).

So to summarize, it can be noted that only a limited number of hydrazines and related structures with antiglycation activity (100 – 1000 μM) were evaluated. It was demonstrated that two hydroxy-substituted phenyl moieties are required for the molecule to be able to inhibit AGE formation because others type of substitution often lead to the loss of antiglycation activity.

Structure 19



19

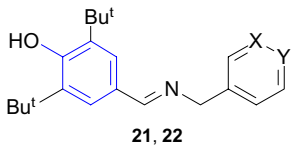
R = Ar, NHPh, Bn

2.3. Phenols and quinones

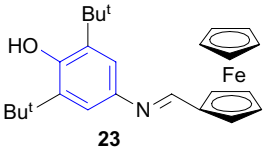
In a number of publications, phenols were used as scaffold with antiglycation activity. Thus, in the series of imino derivatives **20**, several compounds were found with IC_{50} in the mid-micromolar range, and it was demonstrated that the presence of a chlorine atom in the *ortho* position leads to a significant enhancement of antiglycation activity of the compound (Table 12).[46]

Some imino-substituted 2,6-di-*tert*-butylphenol derivatives **21** and **22** promoted the glycation; however, the corresponding ferrocene **23** completely inhibited the glycation (100%) at a concentration of 1000 μM.[47] The IC50 value for compound **23** is 277.1 μM.

Structures 21 – 23



21, **22**

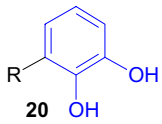


23

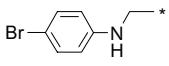
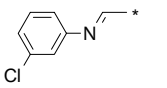
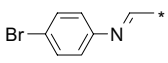
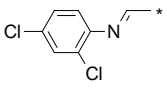
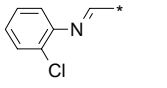
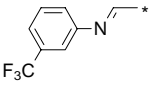
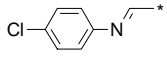
21: X = CH, Y = N
22: X = N, Y = CH

More recently,[48] diphenylsulfimides **24** and **25** were synthesized, but these compounds did not show statistically significant antiglycation activity (31.2% and 13.1% inhibition of AGE formation at a concentration of 1000 μM for compounds **24** and **25**, respectively).

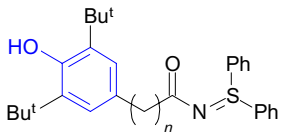
Table 12. Antiglycation activity of compounds **20**.[46]



20

R	$IC_{50} \pm SEM$, μM	R	$IC_{50} \pm SEM$, μM
	440.01 ± 12.71		272.10 ± 11.71 (**20a**)
	43.39 ± 2.37		< 16
	< 16		71.672 ± 4.16
	54.82 ± 1.66		

Structures 24, 25

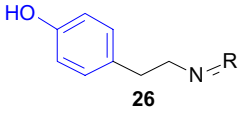


24, **25**

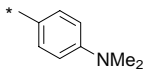
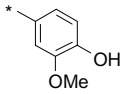
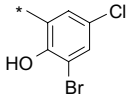
n = 0 (**24**), 2 (**25**)

Schiff bases **26** derived from tyramine exhibited antiglycation activity in the high micromolar range.[49]

Structure 26

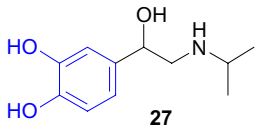


26

R			
IC_{50}, μM	505.27 ± 6.0	581.87 ± 5.50	440.53 ± 2.74

Meanwhile, isoprenaline **27**, containing two hydroxyl groups and related to tyramine, showed antiglycation activity in the glucose–bovine serum albumin (BSA) system with IC_{50} = 70 μM.[50]

Structure 27

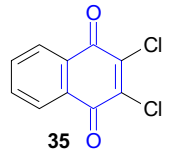


27

Schiff bases **28**–**34** containing phenol and polyphenol moieties were synthesized and evaluated for antiglycation activity.[51] The authors stated that several compounds, in particular **30**–**34**, showed the half-maximal inhibitory concentration in the nano- to yoctomol L^{-1} range.

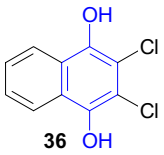
Phenol derivatives, such as quinones, were evaluated for antiglycation activity. Thus, Abbas *et al.*[52] reported that naphthoquinones **35**–**40** and halogenated quinones **41**–**43** can inhibit the formation of AGEs. It was noted that the annulation of the benzene ring to quinone and the introduction of the trifluoromethanesulfonic moiety are favourable for the enhancement of antiglycation activity. Besides, the bromine-containing molecules are generally more active than the corresponding chlorine-containing derivatives.

Structures 35–43



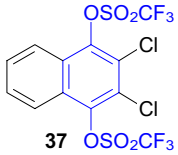
35

IC_{50} = 54 ± 0.2 μM



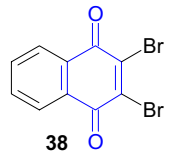
36

IC_{50} = 139 ± 1.352 μM



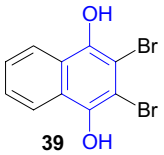
37

IC_{50} < 16 μM



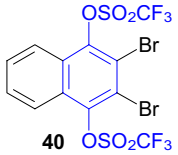
38

IC_{50} = 43 ± 0.5 μM



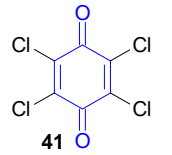
39

IC_{50} = 65 ± 1.00 μM



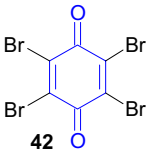
40

IC_{50} < 16 μM



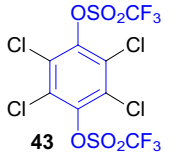
41

IC_{50} = 108 ± 1.5 μM



42

IC_{50} = 101 ± 1.5 μM



43

IC_{50} = 60 ± 1.25 μM

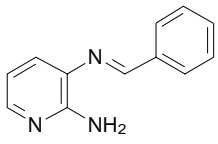
Other quinones **44** and benzoquinones **45** also exhibited antiglycation action in the mid-micromolar range;[53] benzoquinone **44a** proved to be the most promising (IC_{50} = 36 μM) (Table 13).

Therefore, a number of phenol and quinone derivatives were found to have antiglycation effect corresponding to the range IC_{50} = 10–100 μM. It is worth noting that the high ability to inhibit AGE formation in the series of phenols is associated with the presence of at least two hydroxyl groups.

2.4. Carbonyl compounds

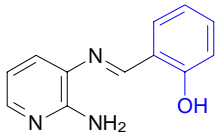
In a number of studies, compounds containing a carbonyl moiety or the closest analogues as the main structural motif were evaluated for antiglycation activity. These studies were

Structures 28–34



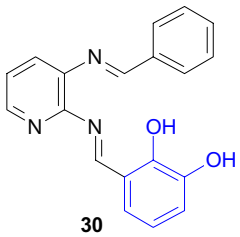
28

IC_{50} = 2.88 × 10^{-1} ± 1.35 μM



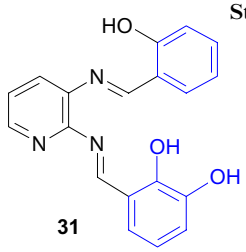
29

IC_{50} = 1.96 × 10^{-1} ± 2.45 μM



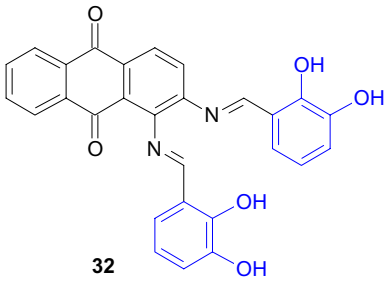
30

IC_{50} = 3.60 × 10^{-7} ± 0.70 μM



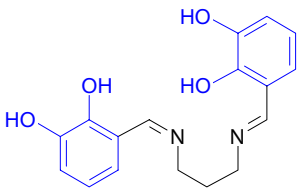
31

IC_{50} = 2.12 × 10^{-10} ± 1.01 μM



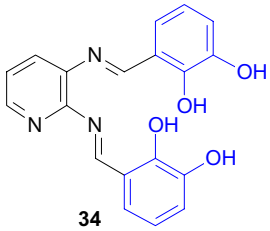
32

IC_{50} = 1.33 × 10^{-11} ± 0.65 μM



33

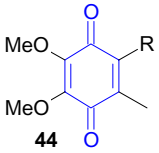
IC_{50} = 4.02 × 10^{-24} ± 0.10 μM



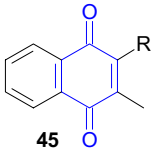
34

IC_{50} = 4.27 × 10^{-11} ± 1.04 μM

Table 13. Antiglycation activity of compounds **44** and **45**.[53]



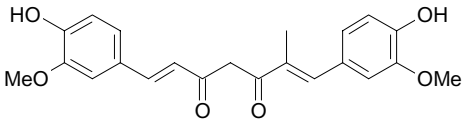
44



45

R	$IC_{50} \pm SEM$, μM	R	$IC_{50} \pm SEM$, μM
COPh	120	Cl	115
Ph	85	Br	98
$CH_2C_6H_4$-4-OBn	83	I	93
$CH_2C_6H_4$-4-OEt	36 (**44a**)		

Curcumin structure

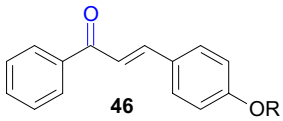


Curcumin

based, in particular, on the fact that the β-dicarbonyl compound curcumin possesses antidiabetic activity.[54]

Naseer and co-workers[55,56] described the ability of 4-alkoxychalcones **46** to inhibit AGE formation depending on the length of the alkyl chain R. It was found that the ethyl group is the substituent of choice (IC_{50} = 89.07 μM) because the shortening or elongation of this substituent leads to a decrease in the antiglycation activity (IC_{50} = 266.82–530.99 μM) or even its loss in the case of the substituent C_{7+}.

Structure 46

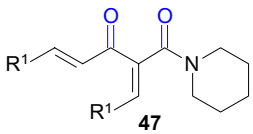


46

R = C_nH_{2n+1};
n = 1–12

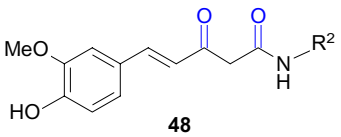
A series of amide analogues of curcumin **47** and **48** were evaluated for antiglycation activity in the study.[57] Twenty compounds were investigated using the structural optimization by varying the substituents R^1 and R^2. However, the activity of all compounds remained in the high micromolar range, and the half-maximal inhibitory concentration of the lead compound (R^2 = C_6H_4-4-SO_2NH_2) was IC_{50} = 118.41 μM.

Structures 47, 48



47

R^1 = (Het)Ar

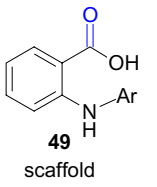


48

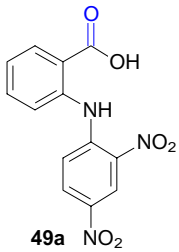
R^2 = Ar

The investigation of *N*-phenylanthranilic acid derivatives **49** demonstrated that the antiglycation activity of compounds with this scaffold is generally observed in the high micromolar range (IC_{50} = 137–597 μM).[58] This kind of activity is directly related to the presence and position of the nitro group in the *N*-phenyl substituent. The presence of this group in the *para* position led to an increase in the ability to inhibit AGE formation. In this study, two lead compounds **49a**,**b** with the half-maximal inhibitory concentration in the mid-micromolar range were found.

Structure 49

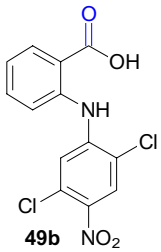


49
scaffold



49a NO_2

IC_{50} = 67.2 ± 0.004 μM

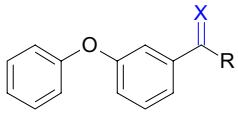


49b NO_2

IC_{50} = 84.8 ± 0.003 μM

In the series of various 3-phenoxy derivatives of benzoic acid **50**, no compounds showed the statistically significant effect on the formation of AGEs at a concentration of 1000 μM compared to aminoguanidine (57.83 ± 0.58% at 1000 μM).[59]

Structure 50



50

X = O, NH, NC(O)Ph;
R = Alk, OAlk, OAr, NHAr

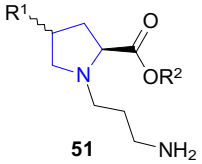
Carbonyl compounds and their closest analogues exhibiting antiglycation activity are scarce in the literature, and most of these compounds have the half-maximal inhibitory concentration higher than 100 μM.

2.5. Non-fused and benzannulated heterocyclic systems

A large number of heterocyclic compounds were evaluated as promising antiglycation agents for the prevention and treatment of late complications of diabetes mellitus. These compounds have attracted attention due to the ability of nitrogen heterocycles to chelate metal ions, which are considered as promoters of glycation.[19] Besides, oxygen-containing heterocycles, primarily synthetic and natural flavonoids, were found to have antioxidant properties and they can chelate metal ions or bind MGO as one of the major intermediate of glycation.[60,61] Therefore, in this and following sections, we consider synthetic small molecules with antiglycation activity containing a heterocycle or more complex fused systems with heteroatoms as the major structural motif.

The antiglycation activity–structure relationship analysis of heterocyclic compounds should be started with non-fused systems. Chilukuri *et al.*[62] investigated *N*-(3-amino-

Structure 51



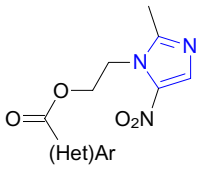
51

R^1 = OH, NH_2, N_3;
R^2 = H, Me

propyl)proline derivatives **51**, which, however, did not show a significant antiglycation effect in the glucose–BSA system. It was found that the hydroxy derivatives exhibited stronger activity compared to azide-containing prolines; however, their activity was in the millimolar range.

4-Nitroimidazole derivatives **52** were evaluated for antiglycation activity by studying the inhibition of AGE formation in the glyoxal–BSA model.[63] The compounds containing a fluorine atom in the aryl substituent proved to be the most active with the half-maximal inhibitory concentration in the high micromolar range (IC_{50} = 218.97–953.42 μM). The presence of other halogen atoms or a nitro group in the aryl moiety or the replacement of this moiety by a hetaryl one led to a decrease in the antiglycation activity or the complete loss of the ability to inhibit AGE formation.

Structure 52

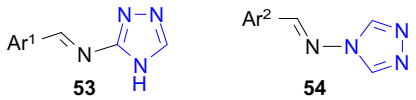


52

More recently, it was demonstrated[64] that C(3)-imine-substituted 1,2,4-triazole derivatives **53** exhibit antiglycation activity in the high micromolar range (IC_{50} = 317.0–586.10 μM).

It was noted that related *N*(4)-substituted heterocycles **54** appeared to be somewhat more active, but the half-maximal inhibitory concentration remained in the high micromolar range (IC_{50} = 248.1–637.7 μM). The compound containing the 2,3-dihydroxyphenyl moiety as the Ar^2 substituent is of particular interest because it has IC_{50} = 47.3 μM.

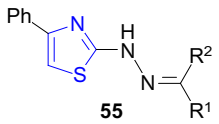
Structures 53, 54



53 **54**

Khan *et al.*[65] evaluated the antiglycation activity of various 2-hydrazino-4-phenylthiazoles **55**. Their half-maximal inhibitory concentrations were in the high micromolar range (IC_{50} = 187.61–886.98 μM). The compounds containing halogen atoms or a hydroxymethyl moiety in the phenyl ring were less active than the corresponding phenols or nitro derivatives.

Structure 55

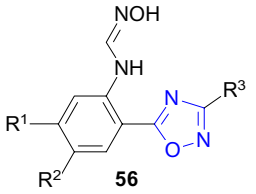


55

R^1 = H, Me;
R^2 = Ar

Okuda *et al.*[66] examined the ability of *N*-[2-([1,2,4]oxadiazol-5-yl)phenyl]formamide oximes **56** to inhibit the formation of pentosidine, which is one of the most well-characterized AGEs. It is worth noting that the evaluation was performed at micromolar concentrations of the compounds (2000 μM). Lead compound **56a**

Structure 56



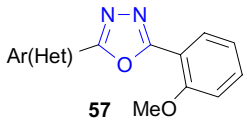
56

R^1 = H, Cl, Me, OMe;
R^2 = H, Cl, NO_2, OMe;
R^3 = H, Me

(R^1 = R^2 = R^3 = H) inhibited the pentosidine formation by 72%, which is indicative of a low potential of these structures as compounds with antiglycation activity.

2-Aryl-1,3,4-oxadiazole derivatives **57** exhibited antiglycation activity in the high micromolar range (IC_{50} = 160.2–495.26 μM). Hydroxyl substituents in the aryl moiety were found to be favourable for an increase in the inhibitory effect against AGEs, while the methyl protection of the hydroxyl group led to the loss of antiglycation effect.[67] The absence of the ability to inhibit AGE formation was observed also for 2-hetaryl-1,3,4-oxadiazoles **57**.

Structure 57



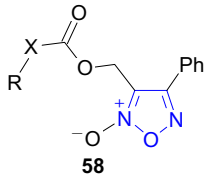
57

Xie *et al.*[68] investigated another type of oxadiazoles, 1,2,5-oxadiazole N-oxides **58**, and examined their antiglycation properties. The successive structural modification made it possible to enhance the antiglycation activity of this scaffold from the millimolar to micromolar range with IC_{50} = 175 μM for lead compound **58a** (Table 14).

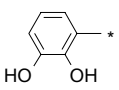
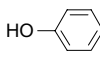
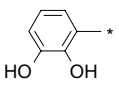
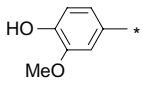
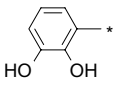
Six-membered nitrogen heterocycles and their benzannulated analogues are another group of compounds with antiglycation activity. Thus, hydroxytyrosol nicotinate **59** showed moderate antiglycation activity (IC_{50} = 270 μM), which is somewhat lower compared to that of aminoguanidine (IC_{50} = 230 μM).[69]

Various thymine and uracil derivatives were evaluated for antiglycation activity. The research group headed by A.A.Spasov[70] demonstrated that heterocyclic scaffold **60**

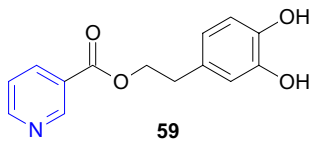
Table 14. Antiglycation activity of compounds **58**.[68]



58

X	R	IC_{50}, μM	X	R	IC_{50}, μM
HC=CH		> 30 000	–		3037
HC=CH		> 30 000	CH_2		386
HC=CH		3259	HC=CH		175 (**58a**)

Structure 59

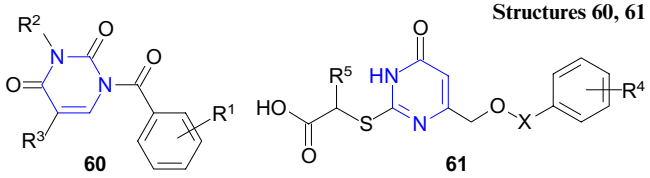


59

had unsatisfactory antiglycation activity. Thus, the AGE formation was inhibited by not more than 35.60% for the lead compound at a concentration of 1000 μM; in some cases, heterocycles **60** even promoted the glycation. Nevertheless, it was noted that the uracil derivatives (R^3 = H) are generally more active than the corresponding substituted thymines (R^3 = Me).

These studies were further developed by performing the screening of 2-thiouracil derivatives **61**.[71] However, these compounds did not show a significant antiglycation effect even at a concentration of 1000 μM (33.35% inhibition of AGE formation for the lead compound) and in some cases, on the contrary, promoted the AGE formation.

Structures 60, 61



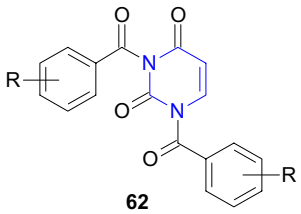
60 **61**

R^1 = OH, OAc, OMe;
R^2 = H, $C(O)C_6H_4OR$;
R^3 = H, Me

R^4 = H, Hal, Me, Ph;
R^5 = H, Me;
X = CH_2, $(CH_2)_2O$

N-Benzoyl derivatives of uracil **62** also did not had a significant effect on the AGE formation at a concentration of 1000 μM. In all cases, their effect was lower compared to that of aminoguanidine, which was used as the reference compound and inhibited AGE formation in the range of 43.4 ± 2.4% at the same concentration.[72]

Structure 62



62

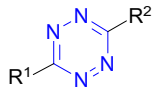
R = OH, OAc, OMe

3,6-Disubstituted 1,2,4,5-tetrazines **63** were synthesized and evaluated for antiglycation activity.[73] It was found that the tetrazines containing the imidazole moiety as the substituent R^1 are more active than the compounds bearing the pyrazole ring (Table 15). However, the heterocycles were investigated at concentrations of 100–1000 μM, which did not allow the consideration of this scaffold as promising to search for compounds with high antiglycation activity.

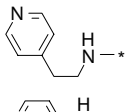
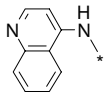
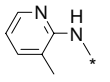
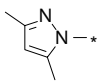
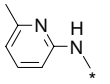
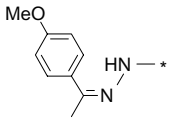
Most of quinoline derivatives **64** did not show the antiglycation effect,[74] or their half-maximal inhibitory concentration was in the high micromolar range (IC_{50} = 282.98–961.50 μM).

Kokil *et al.*[75] synthesized compounds **65** containing the dibenzoazepine moiety bonded to various benzoyl moieties through the 1,2,3-triazole linker and examined their ability

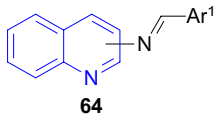
Table 15. Antiglycation activity of compounds **63**.[73]



63

R^1	R^2	Inhibition of AGE formation (%)	
		M = 1000 μM	M = μM
NHPh	OMe	67.32 ± 1.42	21.09 ± 2.68
	$NH(CH_2)_6Me$	75.11 ± 1.60	31.22 ± 2.15
		69.29 ± 1.25	17.61 ± 4.05
		89.90 ± 0.86	40.74 ± 5.09
		−82.30 ± 12.78	−40.26 ± 11.14
		47.43 ± 6.89	12.49 ± 6.56
	$NH(CH_2)_{10}Me$	21.98 ± 8.05	12.08 ± 7.46

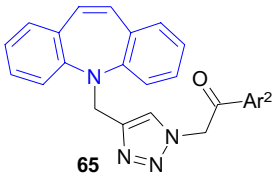
Structure 64



64

to inhibit AGE formation. However, in all cases the inhibition was not higher than 30% at a concentration of 1000 μM regardless of the type of substitution in the benzoyl moiety.

Structure 65



65

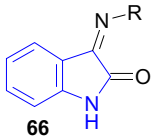
The evaluation of the antiglycation activity of non-fused heterocycles and their benzannulated analogues involved nitrogen-containing compounds, such as oxadiazoles, thiazoles, pyridines, pyrimidones, symmetric tetrazines and certain quinolines and dibenzoazepines. In all cases, a low antiglycation activity in the high micromolar range was observed regardless of the nature of substituents on the heterocyclic scaffold, which is indicative of a low potential of compounds of this series as active inhibitors of AGE formation.

2.6. Isatin and benzimidazole derivatives

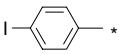
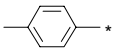
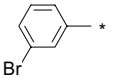
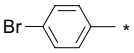
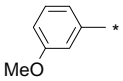
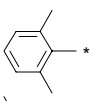
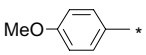
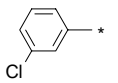
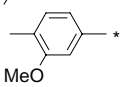
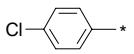
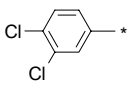
Indole and benzimidazole derivatives and related structures occupy a significant niche among heterocyclic compounds with antiglycation activity. Thus, the reaction of various anilines with isatin afforded Schiff bases **66**, which were evaluated for antiglycation activity relative to aminoguanidine (IC_{50} = 268.7 ± 12.4 μM) (Table 16). The compounds containing a halogen atom in the *meta* position of the substituent R showed moderate antiglycation activity, whereas all other heterocycles were recognized to be inactive.[76]

In continuation of studies of this series of Schiff bases, Choudhary and co-workers[77] synthesized imines **67** and investigated the effect of substituents both in the terminal phenyl moiety R^4 and in the isatin scaffold on the antiglycation activity. It was found that the compounds containing a nitro group in the aryl moiety R^4 have the highest inhibitory effect against AGE formation (IC_{50} = 243.95 – 257.61 μM). However, even in this case, the half-maximal inhibitory concentration was in the high micromolar range. Besides, the presence of chlorine atoms in the benzazole moiety ($R^1 - R^3$) generally leads to complete loss of antiglycation activity. This effect was particularly pronounces in the structures containing free hydroxyl in the substituent R^4.

Table 16. Antiglycation activity of compounds **66**.[76]

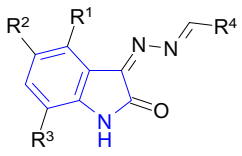


66

R	Inhibition of AGE formation [a] (%)	R	Inhibition of AGE formation [a] (%)
	53.6		61.8
	56.1		64.6
	65.3		62.2
	46.7		77.0 (177.2 ± 0.4) [b]
	56.0		58.0
	53.2		54.7
	51.0		56.3
	60.0		50.3
	71.30 (675 ± 0.12) [b]		26.9
	40.9		69.1

[a] M = 20 μM, [b] IC_{50} ± SEM, μM.

Structure 67

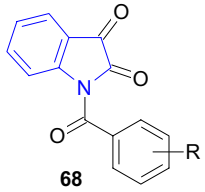


67

R^1, R^2, R^3 = H, Cl;
R^4 = Ar

More recently, *N*-benzoyl derivatives of isatin **68** were evaluated for antiglycation activity and structure — activity relationships were found (Table 17).[78] It was demonstrated that the presence of a *para* substituent in the benzoyl moiety results in the loss of antiglycation activity except for nitro derivative **68b**. Heterocycle **68a** containing the unsubstituted benzoyl moiety proved to be the most active (IC_{50} = 18.01 ± 0.05 μM).

Table 17. Antiglycation activity of compounds **68**.[78]

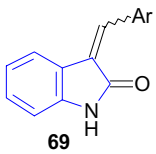


68

R	IC_{50} ± SEM, μM	R	IC_{50} ± SEM, μM
H	18.01 ± 0.05 **(68a)**	3-Cl	117.91 ± 2.9
2-Me	693.7 ± 3.0	4-Cl	72.5 ± 0.09
3-Me	170.2 ± 0.62	2-OMe	NA
4-Me	NA	4-OMe	NA
2-NO_2	NA	2-F	171.3 ± 0.79
3-NO_2	555 ± 11.0	3-F	483 ± 11.0
4-NO_2	80.18 ± 0.07 **(68b)**	4-Br	NA
2-Cl	NA		

Some indol-2-one derivatives **69** exhibited antiglycation activity in the high micromolar range (IC_{50} = 150.4 – 856.71 μM). It was found that a somewhat higher ability to inhibit AGE formation is associated with the presence of a fluorine atom in the *para* position of the phenyl moiety Ar, a chlorine atom in the *meta* position or a hydroxyl group.[79]

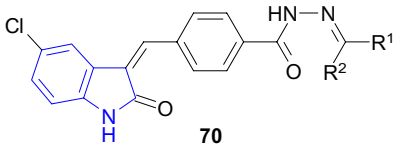
Structure 69



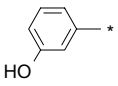
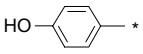
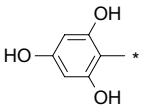
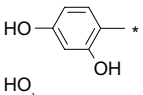
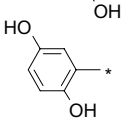
69

In the series of 5-chloroindol-2-one derivatives **70**, an increase in the number of hydroxyl groups on the phenyl moiety R^1 leads to the enhancement of antiglycation activity (Table 18).[80] The presence of a methyl group as the substituent R^2 results in a decrease in this activity due apparently to steric hindrance. Besides, the methylation of the hydroxyl group leads causes the loss of antiglycation activity. On the whole, all active compounds showed the

Table 18. Antiglycation activity of compounds **70**.[80]



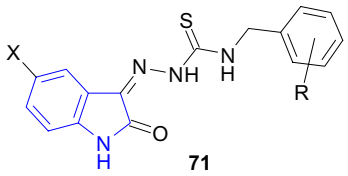
70

R^1	$IC_{50} \pm SEM$, μM	
	$R^2 = H$	$R^2 = Me$
	559.37 ± 2.12	NA
	466.54 ± 3.88	843.99 ± 3.23
	155.22 ± 2.98	336.96 ± 3.42
	195.95 ± 0.43	NA
	289.47 ± 2.47	NA

half-maximal inhibitory concentration only in the high micromolar range (IC_{50} = 155.22 – 843.99 μM).

Pervez *et al.*[81,82] modified isatin and 5-chloroisatin to prepare thiosemicarbazones **71**, which exhibited antiglycation activity in the high micromolar range. They found that the 5-chlorine-substituted derivatives are generally more active than isatins containing no halogen atoms. Besides, the authors estimated the effect of substituents in the phenyl moiety. The heterocycle containing a methyl group in the *meta* position proved to be the most efficient. The replacement of the methyl group by a fluorine atom led to a slight decrease in the antiglycation activity; the presence of a chlorine atom or a methoxy group in this position caused a significant increase in the IC_{50} value (Table 19).

Table 19. Antiglycation activity of compounds **71**.[81,82]

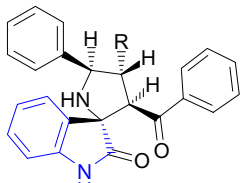


71

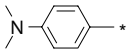
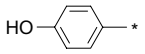
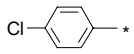
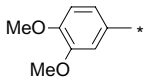
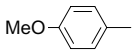
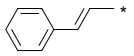
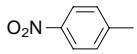
R	$IC_{50} \pm SEM$, μM	
	X = H	X = Cl
H	NA	NA
2-Me	605.26 ± 2.24	333.06 ± 9.80
3-Me	231.70 ± 6.71	114.51 ± 1.08
4-Me	209.87 ± 0.37	NA
2-OMe	NA	NA
3-OMe	522.68 ± 9.10	NA
4-OMe	NA	229.94 ± 3.40
2-F	224.34 ± 0.47	202.21 ± 0.55
3-F	NA	168.71 ± 8.58
4-F	217.94 ± 1.98	343.75 ± 2.76
2-Cl	228.55 ± 2.30	NA
3-Cl	NA	433.88 ± 2.66
4-Cl	NA	217.71 ± 1.65
2,4-$(Cl)_2$	NA	NA
3,4-$(Cl)_2$	NA	NA

Kaur *et al.*[83] synthesized 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2,3-indolin]-2-ones **72** by the cycloaddition reaction and found several compounds with antiglycation activity in the low to mid-micromolar range. Heterocycle **72a** containing the unsubstituted phenyl moiety was a lead compound, whereas the presence of a substituent on the phenyl ring or an ethylene bridge between the heterocyclic system and the benzene moiety caused a decrease in the antiglycation effect (Table 20).

Table 20. Antiglycation activity of compounds **72**.[83]



72

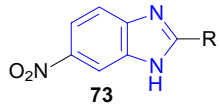
R	$IC_{50} \pm SEM$, μM	R	$IC_{50} \pm SEM$, μM
	11.37 ± 0.52 (**72a**)		57.31 ± 2.56
	104.49 ± 1.78		19.57 ± 1.31
	111.45 ± 3.02		21.21 ± 0.91
	20.67 ± 3.63		97.77 ± 3.64
	39.67 ± 1.42		

Benzimidazoles related to isatin and its derivatives were also found to be able to inhibit AGE formation. Thus, compounds containing polyphenol moieties exhibited the highest antiglycation activity in the series of 2-(het)aryl-6-nitrobenzimidazoles **73**, heterocycles with two hydroxyl groups, particularly those containing one hydroxyl group in the *meta* position, being the most active (Table 21).[84]

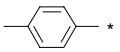
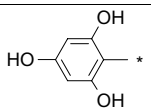
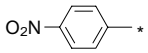
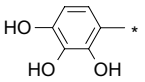
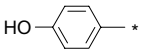
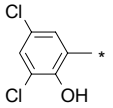
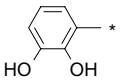
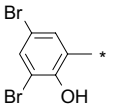
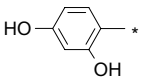
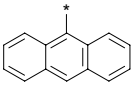
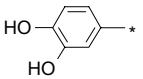
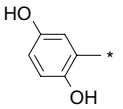
Khan and co-workers[85] evaluated the antiglycation activity of a series of substituted 4-methylbenzimidazoles **74**. These compounds were found to be active in the high micromolar range (IC_{50} = 140.40 – 500.65 μM). It was emphasized that the heterocycles containing phenol moieties were the most effective inhibitors of AGE formation. The methylation of the hydroxyl group led to a decrease in the antiglycation activity, and the replacement of the aryl moiety Ar by the hetaryl moiety HetAr resulted in the loss of antiglycation activity.

The presence of a phenol moiety in the series of 2-aryl-4,6-dichlorobenzimidazoles **75** is also important for the manifestation of antiglycation properties because the replacement of the free hydroxyl group by the methoxy group in the aryl moiety or the presence of other substitu-

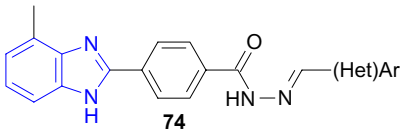
Table 21. Antiglycation activity of compounds **73**.[84]



73

R	IC_{50}, μM	R	IC_{50}, μM
	192 ± 0.017		109 ± 0.001
	114 ± 0.005		71.7 ± 0.008
	194 ± 0.039		892 ± 0.001
	17.7 ± 0.001		63 ± 0.002
	52.4 ± 0.001		37.5 ± 0.033
	25.5 ± 0.001		142 ± 0.014
	48.7 ± 0.006		

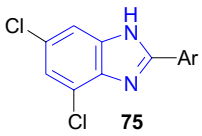
Structure 74



74

ents leads to a decrease in this kind of activity.[86] However, even the most active compounds of this series showed the half-maximal inhibitory concentration in the high micromolar range (IC_{50} = 182.30 – 473.51 μM).

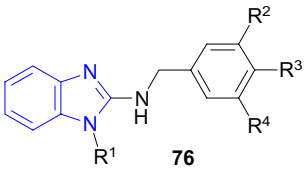
Structure 75



75

The research team headed by A.A.Spasov[87] synthesized a series of 1-alkyl-2-benzylaminobenzimidazoles **76**. Despite the variation of both the alkyl group R^1 and the substituents $R^2 - R^4$ in the benzyl moiety, this scaffold did not show

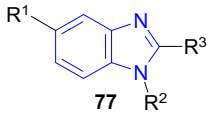
Structure 76



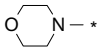
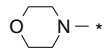
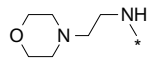
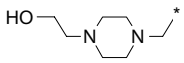
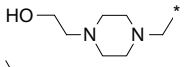
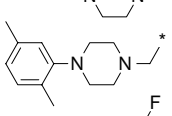
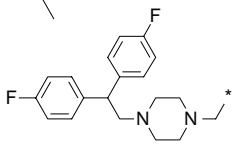
76

R^1 = Alk, $AlkNR_2$;
R^2, R^3, R^4 = H, OMe

Table 22. Antiglycation activity of compounds **77**.[88]



77

R^1	R^2	R^3	Inhibition of AGE formation (%) (M = 1000 μM)
H	$CH_2CH{=}CH_2$		94.1 ± 1.26 (**77a**)
H			89.7 ± 2.17 (**77b**)
H	Bn		45.5 ± 1.29
H	Bn		54.4 ± 2.57
H	H		−16.6 ± 0.34
Me	Me		−15.8 ± 0.76
Me	Me		0.5 ± 4.51
OMe	Me		−9.4 ± 6.59
OMe	Me		−15.2 ± 2.71
OMe	Me		−36.1 ± 11.08

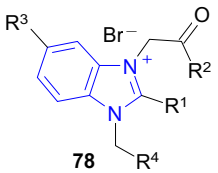
the statistically significant antiglycation effect at a concentration of 1000 μM.

In later studies, the series of 1-alkylbenzimidazoles was extended due to the synthesis of heterocycles **77** (Table 22), among which two compounds (**77a**,**b**) were found to be effective inhibitors of AGE formation at a concentration of 1000 μM; both these heterocycles contain morpholine in the C(2) position.[88]

The activity of 2-amino- and 2-hydroxymethylbenzimidazolyl bromides **78** against diabetes-associated targets was evaluated in a recent study.[89] Heterocycles **78** were tested for antiglycation activity. It was demonstrated that this scaffold does not have a significant inhibitory effect against AGE formation. Only the heterocycle containing the 2,6-di-*tert*-butylphenol moiety R^2 showed the half-maximal inhibitory concentration in the high micromolar range (IC_{50} = 193.36 μM).

In the series of trifluoromethyl derivatives of pyrrolo[1,2-*a*]benzimidazoles **79**, there were no compounds

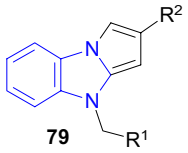
Structure 78



78

R^1 = NH_2, CH_2OH;
R^2 = Ar; R_3 = H, OMe
R^4 = H, Me, C_6H_4-4-C_6H_5, C_6H_4-4-C_6H_4-2-COOH

Structure 79



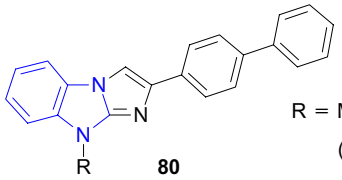
79

R^1 = $AlkNR'_2$
(R' = Et, $(CH_2)_5$, *etc.*);
R^2 = CF_3, C_6H_4-4-CF_3

with potential antiglycation activity. All structures showed lower activity compared to aminoguanidine used as the reference compound.[90]

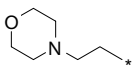
The annulation of the pyrrole moiety to benzimidazole giving 2-(biphenyl-4-yl)imidazo[1,2-*a*]benzimidazoles **80** also did not afford molecules with promising antiglycation activity. On the contrary, compounds containing a simple alkyl moiety promoted the interaction of glucose with BSA.[91]

Structure 80



80

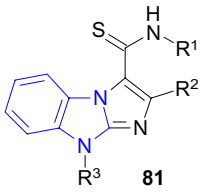
R = Me, Et, Bu^n,
$(CH_2)_2NEt_2$,



The introduction of the thioamide moiety into imidazo[1,2-*a*]benzimidazoles gave compounds **81** with the half-maximal inhibitory concentration in the mid-micromolar range (Table 23). It was found that the *para*-chlorophenyl moiety R^3 bound to the N(9) atom plays an important role in the antiglycation activity.[92]

Subsequently, this research group[93] extended the series of fused benzimidazoles **82**, in particular by increasing the size of the fused moiety. However, only a few compounds showed a moderate ability to inhibit AGE formation at a concentration of 1000 μM ($\leqslant 38.5 \pm 4.3\%$).

Table 23. Antiglycation activity of compounds **81**.[92]

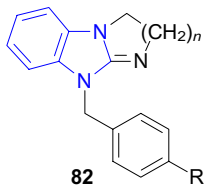


81

R^1	R^2	R^3	Inhibition of AGE formation (%) (M = 1000 μM)
Et	Pr^n	Me	90.6 ± 6.0 (88.06) [a]
Et	Bn	Me	17.8 ± 6.7
Ph	Me	Me	NA
Ph	Bu^n	Me	NA
Ph	Bn	Me	NA
Ph	$CH_2CH{=}CH_2$	Me	NA
Ph	Me	Ph	NA
Ph	$CH_2CH{=}CH_2$	Ph	4.7 ± 3.8
Ph	Bu^n	Ph	18.4 ± 16.4
Ph	Me	C_6H_4-4-Cl	88.8 ± 11.2 (64.24) [a]
Ph	Et	C_6H_4-4-Cl	100.0 ± 0.0 (101.40) [a]
$CH_2CH{=}CH_2$	Me	$CH_2CH{=}CH_2$	41.5 ± 9.7
$CH_2CH{=}CH_2$	Pr^n	Me	NA
$CH_2CH{=}CH_2$	Bn	Me	NA

[a] IC_{50}, μM.

Structure 82

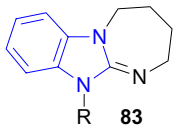


82

n = 1–3;
R = COOR′
(R′ = CO_2H, CO_2Et),
C_6H_4-2-X (X = CN,
CO_2H, CO_2Me и др.)

In the series of fused 2,3,4,5-tetrahydro[1,3]diazepino[1,2-*a*]benzimidazole derivatives **83**, no compounds with antiglycation activity were discovered; on the contrary, most of these heterocycles promoted glycation.[94]

Structure 83



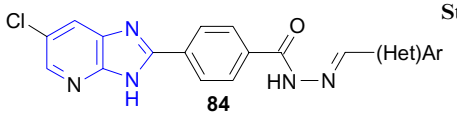
83

$\cdot n$HX

X = Cl, Br; n = 1, 2;
R = $AlkNR'_2$ (R′ = Et, $(CH_2)_2$,
$(CH_2)_3$, *etc.*),
AlkAr (Alk = CH_2, $(CH_2)_2$, $(CH_2)_2O$)

Imidazo[4,5-*b*]pyridines **84** were synthesized by the modification of the benzimidazole scaffold with the aim of discovering compounds with antidiabetic, in particular antiglycation, activity. Taha *et al.*[95] synthesized a number of compounds with activity in the high micromolar range (IC_{50} = 140.12–420.12 μM) by varying the aryl moiety in the side chain. In most cases, the activity appeared in the presence of the hydroxyl moiety in the substituent (Het)Ar.

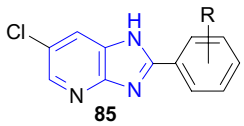
Structure 84



84

In the related series of 6-chloro-2-(het)arylimidazo[4,5-b]pyridines **85**, several heterocycles also exhibited antiglycation activity in the high micromolar range (IC_{50} = 210.12–320.20 μM), and it was found that the presence of a phenol or polyphenol substituent at the C(2) position of the heterocyclic systems is necessary for the manifestation of this effect.[96]

Structure 85

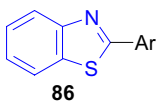


85

R = 2-OH, 3-OH,
2,4-$(OH)_2$, 3,4-$(OH)_2$, *etc.*

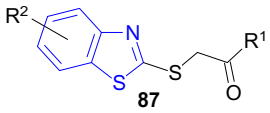
A number of publications concerned with indole and benzimidazole derivatives, in which nitrogen is replaced by other heteroatoms. In particular, only five compounds of benzo-1,3-thiazole series **86** exhibited antiglycation activity in the high micromolar range (IC_{50} = 190–1740 μM), the

Structure 86

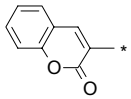
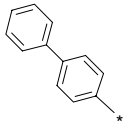


86

Table 24. Antiglycation activity of compounds **87**.[98]



87

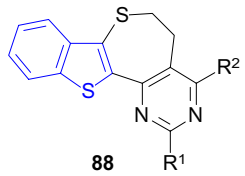
R^1	$IC_{50} \pm SEM$, μM			
	R^2			
	H	6-NH_2	5-Cl	6-OEt
C_6H_4-4-NO_2	377 ± 1.9	ND	NA	NA
C_6H_4-4-OMe	260 ± 5.4	ND	472 ± 2.4	ND
C_6H_4-4-Cl	509 ± 3.3	224 ± 1.9	226 ± 1.6	NA
C_6H_4-4-Br	NA	ND	416 ± 3.6	NA
C_6H_4-3-Br	452 ± 2.8	238 ± 2.2	397 ± 5.7	NA
C_6H_4-3-OH	484 ± 7.3	223 ± 3.3	424 ± 4.7	NA
C_6H_4-2-OMe	595 ± 3.7	ND	ND	ND
C_6H_4-3-OMe	925 ± 12.2	187 ± 2.6	471 ± 5.7	416 ± 8.7
	500 ± 5.3	707 ± 2.1	331 ± 1.6	471 ± 2.5
	342 ± 3.1	219 ± 3.6	274 ± 2.4	365 ± 4.9

heterocycle bearing the *para*-dimethylaminophenyl substituent Ar being the most active one.[97]

In the series of benzo-1,3-thiazoles **87**, the substituent R^2 in the benzannulated moiety of the heterocycle exerts a significant effect on the antiglycation activity. Thus, the replacement of an amino group or a chlorine atom by the hydroxyethyl moiety leads to the loss of this kind of activity (Table 24).[98] The nature of the aryl group R^1 in the side chain has a somewhat weaker effect on the activity. Thus, despite different types of replacement, the half-maximal inhibitory concentration was in the high micromolar range.

The evaluation of the antiglycation effect of 5,6-dihydro[1]benzothieno[3′,2′:2,3]thiepino[4,5-*d*]pyrimidines **88** demonstrated that all compounds of this series inhibit the formation of pentosidine (a representative of AGEs) by less than 20% at a concentration of 2000 μM.[99]

Structure 88



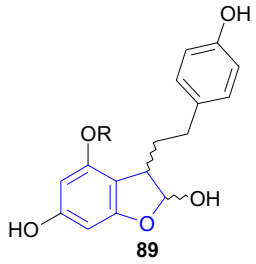
88

R^1 = H, Me, Et, Ph, C_6H_4Me-4;
R^2 = NHMe, NHEt, NMe_2, $NH(CH_2)_2OH$, $S(CH_2)_2OH$, $O(CH_2)_2OH$

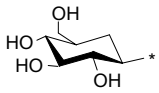
Besides, the replacement of a nitrogen atom in indole by oxygen affords scaffold **89** with high inhibitory potential against AGE formation (Table 25).[100]

Related phenyl-containing 2,3-dihydrobenzofurans **89** showed antiglycation activity in the low to mid-micromolar range. It should be noted that the *cis* derivatives were found to be more active compared to the *trans* derivatives.[100]

Table 25. Antiglycation activity of compounds **89**.[100]



89

R	Configuration	$IC_{50} \pm SEM$, μM	R	Configuration	$IC_{50} \pm SEM$, μM
H	9R,10S	29.2 ± 1.3		9R,10S	9.1 ± 0.5 (**89a**)
	9S,10R	39.9 ± 1.5		9S,10R	13.8 ± 0.7

The following structure—activity relationships were established in the series of indoles, benzimidazoles and related heterocycles (Fig. 4):

— the presence of a chlorine atom at the C(5) position or a nitro group at the C(6) position of the benzannulated moiety generally leads to the enhancement of antiglycation activity;

— the acylation of the N(1) atom in indoles is applicable to searching for compounds with a high antiglycation effect; on the contrary, the alkylation or acylation of the nitrogen atom N(1) in benzimidazoles leads to a decrease in the ability to inhibit AGE formation;

— lower half-maximal inhibitory concentrations in the series of benzimidazoles are observed for compounds, in which the heterocyclic scaffold is directly attached to the phenyl moiety through a C—C bond. The presence of a linker between the heterocycle and the phenyl substituent reduces the antiglycation effect;

— the replacement of benzimidazole by benzothiazole decreases the antiglycation effect; on the contrary, 2,3-dihydrobenzofuran derivatives belong to lead compounds;

— the annulation of (het)aryl moieties to benzimidazole results, with rare exceptions, in the loss of antiglycation activity.

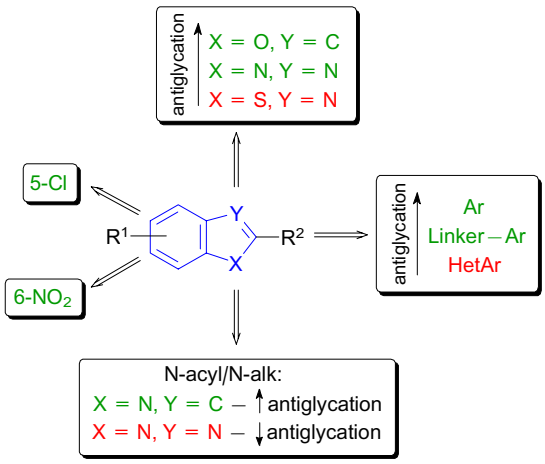


Figure 4. Structure–activity relationship for the scaffold of isatins/benzimidazoles and related derivatives.

2.7. Benzopyranones and their derivatives

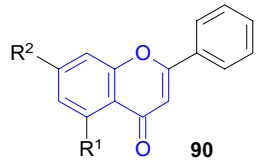
Coumarins and other benzopyranones were also evaluated for the ability to inhibit AGE formation because, as mentioned previously, the antiglycation activity is often associated with the antioxidant effect. Coumarins are considered as natural and synthetic antioxidants.[101] Thus, some chrysin derivatives **90** containing a nitrooxy group in the side chain exhibited antiglycation activity in the mid-micromolar range (Table 26). The activity decreases with increasing length of the alkyl chain. Besides, the structures containing no ester groups in the side chain did not show the inhibitory activity in the glucose–BSA system.[102]

The evaluation of a series of chrysin derivatives **91** demonstrated that diacetyl derivative **91a** exhibited antiglycation activity in the low micromolar range, whereas the IC_{50} values for some other heterocycles **91** are in the range of 21.61–31.78 μM, which is indicative of the prospects of this scaffold (Table 27).[103]

Flavones **92** showed antiglycation activity in the mid- to high micromolar range (Table 28); however, it was impossible to establish the structure—activity relationship in the series of four compounds.[104]

The variation of the amino moiety during the synthesis of a series of 2-(*para*-hydroxymethylphenyl)-7-(2-aminoethoxy)benzopyran-4-ones **93** demonstrated that the six-membered cyclic amines (morpholine, substituted piperazines) are beneficial for the antiglycation activity compared to the five-membered moieties (pyrrole, imidazole).[105]

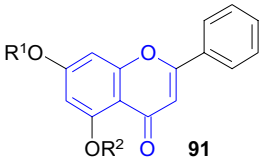
Table 26. Antiglycation activity of compounds **90**.[102]



90

R^1	R^2	$IC_{50} \pm SEM$, μM	R^1	R^2	$IC_{50} \pm SEM$, μM
OH	OH	63.54 ± 6.42	OH	$O(CH_2)_4ONO_2$	75.5 ± 8.07
OH	$OCH_2C(O)O(CH_2)_2ONO_2$	43.89 ± 6.76	OH	$O(CH_2)_6ONO_2$	⩾300
OH	$OCH_2C(O)O(CH_2)_4ONO_2$	52.47 ± 3.73	OAc	$O(CH_2)_2ONO_2$	⩾300
OH	$OCH_2C(O)O(CH_2)_6ONO_2$	137.6 ± 8.86	OAc	$O(CH_2)_4ONO_2$	⩾300
OH	$O(CH_2)_2ONO_2$	⩾300	OAc	$O(CH_2)_6ONO_2$	⩾300

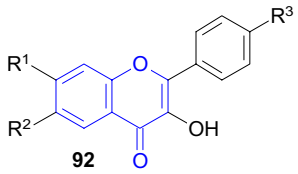
Table 27. Antiglycation activity of compounds **91**.[103]



91

R^1	R^2	$IC_{50} \pm SEM$, μM	R^1	R^2	$IC_{50} \pm SEM$, μM
H	H	24.96	Me	H	>200
Ac	H	21.61	Me	Me	31.78
Ac	Ac	0.91 (**91a**)	$CH_2CH{=}CMe_2$	H	>200

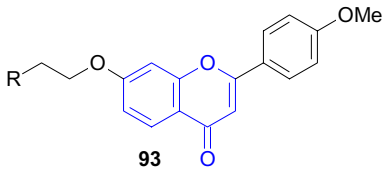
Table 28. Antiglycation activity of compounds **92**.[104]



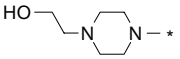
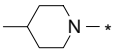
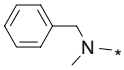
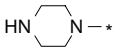
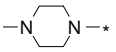
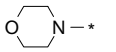
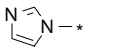
92

R^1	R^2	R^3	$IC_{50} \pm SEM$, μM
H	H	NMe_2	140.02 ± 8.40
OH	H	NMe_2	99.94 ± 4.92
H	Me	Me	219.01 ± 16.25
H	H	Et	196.05 ± 13.78

Table 29. Antiglycation activity of compounds **93**.[105]



93

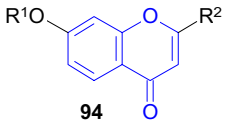
R	$IC_{50} \pm SEM$, μM	R	$IC_{50} \pm SEM$, μM
	36.76 ± 1.51		64.03 ± 1.90
	43.53 ± 0.85		69.33 ± 2.04
NEt_2	50.36 ± 0.65		72.92 ± 1.25 (**93b**)
	51.16 ± 1.40 (**93a**)		80.23 ± 2.21
	56.33 ± 0.94		113.14 ± 1.05
NMe_2	75.23 ± 1.02		

Besides, structure **93b** containing the unsubstituted piperazine ring is less active than its *N*-substituted analogue **93a** (Table 29).

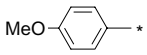
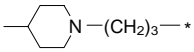
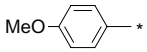
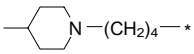
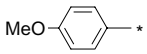
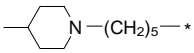
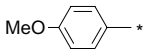
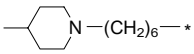
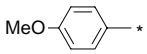
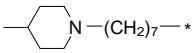
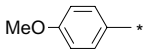
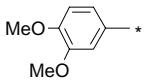
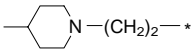
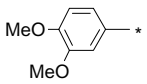
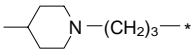
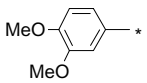
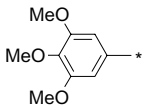
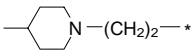
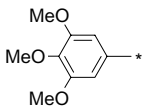
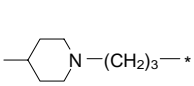
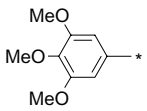
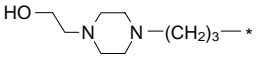
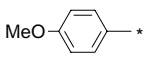
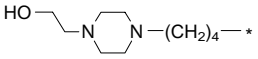
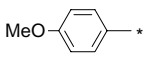
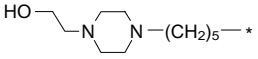
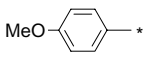
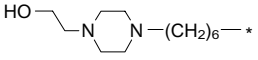
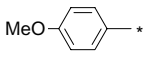
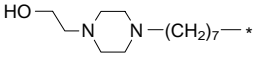
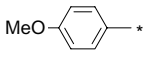
2-Methoxyphenylbenzopyran-4-ones **94** exhibited rather high antiglycation activity in the range IC_{50} = 37.12–61.64 μM. Some structure–activity relationships were revealed for this series of compounds. Thus, it was found that alkoxypiperazine derivatives are more active than the corresponding methylpiperidines (Table 30). An increase in the length of the alkyl linker between benzopyran and piperazine/piperidine leads to a decrease in the antiglycation activity, the C_2–C_4 alkyl being the linker of choice. The number of methoxy groups in the C(2)-phenyl moiety R^2 has only a slight effect on this kind of activity.[106]

The evaluation of the antiglycation activity of substituted 2-phenylchromon-4-ones **95** allowed the conclusion that the introduction of hydroxyls at the C(5) and C(7) positions of the benzopyran system leads to an increase in the ability to inhibit AGE formation (Table 31). On the other hand, the *meta*-substitution of the C(2)-phenyl moiety is preferable over the *para* substituents for a more pronounced antiglycation effect.[107]

Table 30. Antiglycation activity of compounds **94**.[106]

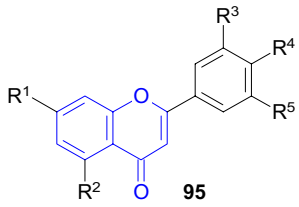


94

R^1	R^2	$IC_{50} \pm SEM$, μM
H		42.0 ± 1.82
		42.60 ± 1.85
		48.24 ± 1.92
		55.12 ± 1.08
		57.23 ± 0.92
		61.64 ± 1.75
H		51.4 ± 0.94
		41.2 ± 0.87
		47.7 ± 1.12
H		47.4 ± 0.94
		37.12 ± 0.98
		41.75 ± 1.41
		43.15 ± 2.19
		38.42 ± 1.46
		49.36 ± 0.85
		50.4 ± 1.85
		52.7 ± 1.84

Jayashree *et al.*[108] investigated the effect of a series of thiophene-containing flavone derivatives **96** as analogues of polyphenols, in particular quercetin (IC_{50} = 1171.27 μM), on the reaction of glucose with BSA. The replacement of the chlorine atom at the C(6) position by bromine was demonstrated to lead to the loss of inhibitory activity (Table 32). The 3-hydroxy derivatives proved to be inactive, whereas the *O*-benzylated compounds demonstrated strong antiglycation activity. Structure **96a** containing the *para*-hydroxymethyl moiety was found to be the lead compound with IC_{50} = 67.59 μM.

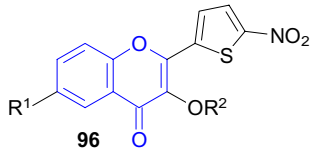
Table 31. Antiglycation activity of compounds **95**.[107]



95

R^1	R^2	R^3	R^4	R^5	$IC_{50} \pm SEM$, μM
H	H	H	H	H	116.5 ± 0.71
H	H	NO_2	H	H	79.0 ± 1.32
H	H	Cl	H	H	91.0 ± 0.17
H	H	F	H	H	77.0 ± 2.11
H	H	H	NO_2	H	118.0 ± 0.85
H	H	H	Cl	H	148.5 ± 3.41
H	H	H	F	H	126.0 ± 0.17
H	H	H	OMe	H	65.5 ± 0.52
H	H	OMe	OMe	OMe	58.0 ± 1.71
H	H	NO_2	H	NO_2	54.0 ± 2.13
OH	H	H	H	H	45.0 ± 2.11
OH	H	H	F	H	55.0 ± 1.2
OH	H	H	OMe	H	42.0 ± 1.82
OH	OH	H	H	H	33.0 ± 1.91

Table 32. Antiglycation activity of compounds **96**.[108]

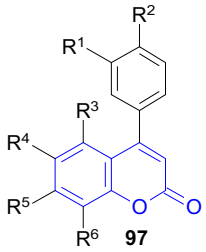


96

R^1	R^2	IC_{50}, μM	R^1	R^2	IC_{50}, μM
Cl	H	NA	Br	H	NA
Cl	Bn-2-Cl	NA	Br	Bn-2-Cl	NA
Cl	Bn-4-Cl	1641.83	Br	Bn-4-Cl	NA
Cl	Bn-2-NO_2	1492.93	Br	Bn-2-NO_2	NA
Cl	Bn-3-NO_2	1039.60	Br	Bn-3-NO_2	NA
Cl	Bn-4-NO_2	741.02	Br	Bn-4-NO_2	> 1900
Cl	Bn-4-F	NA	Br	Bn-4-F	NA
Cl	Bn-4-OMe	67.59 (**96a**)	Cl	Bn-2-F	530.31
Cl	Bn-3-Cl	1338.45	Cl	Bn-4-Me	397.33

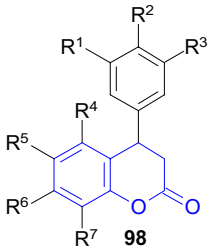
Wang *et al.*[109] evaluated the antiglycation activity of a wide range of 4-polyphenolic coumarins **98** and their 3,4-dihydro derivatives **97** in order to establish structure—activity relationships (Table 33). It was demonstrated that 3,4-dihydro derivatives **97** exhibited lower antiglycation activity compared to their aromatic analogues **98**. Besides, the presence of the hydroxyl group in the *meta* or *para* position of the C(4)-phenyl ring is required for the pronounced antiglycation effect. It is worth noting that the presence of at least two substituents on the benzene ring of coumarin is important for the activity because the 6- and 7-hydroxy derivatives did not exhibit high antiglycation activity, except for compound **98a** (IC_{50} = 5.38 ± 0.13 μM). 1′,2′,6,8-Tetrahydroxycoumarin **98b** with IC_{50} = 1.64 ± 0.10 μM was found to be the lead compound.

Table 33. Antiglycation activity of compounds **97** and **98**.[109]



97

R^1	R^2	R^3-R^6	$IC_{50} \pm SEM$, μM
H	OMe	7-OH	> 3700
OMe	OMe	7-OH	174.48 ± 4.58
OMe	OH	7-OH	682.98 ± 53.63
H	OMe	6-OH	> 3700
OMe	OMe	6-OH	> 3700
H	OMe	7,8-$(OH)_2$	261.06 ± 1.48
OH	OMe	7,8-$(OH)_2$	99.02 ± 6.03
OMe	OH	7,8-$(OH)_2$	404.26 ± 23.54
OMe	OMe	7,8-$(OH)_2$	21.43 ± 0.86
H	OMe	5,7-$(OH)_2$	> 3700
H	OH	5,7-$(OH)_2$	> 3700
OH	OMe	5,7-$(OH)_2$	> 3700
OMe	OMe	5,7-$(OH)_2$	24.58 ± 0.77
OMe	OH	5,7-$(OH)_2$	18.57 ± 0.88
OH	OH	5,7-$(OH)_2$	16.60 ± 1.35
OMe	OMe	6,8-$(OH)_2$	20.55 ± 0.29

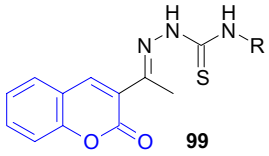


98

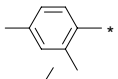
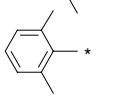
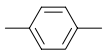
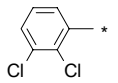
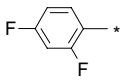
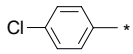
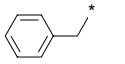
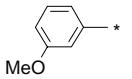
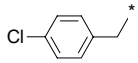
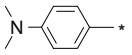
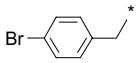
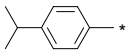
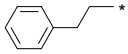
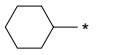
R^1	R^2	R^3	R^4-R^7	$IC_{50} \pm SEM$, μM
H	OMe	H	7-OH	> 3700
OMe	OMe	H	7-OH	5.38 ± 0.13 (**98a**)
OH	OH	H	7-OH	> 3700
H	OMe	H	7,8-$(OH)_2$	7.95 ± 2.18
H	OH	H	7,8-$(OH)_2$	89.63 ± 4.70
OH	OH	H	7,8-$(OH)_2$	2.16 ± 0.06
OH	OH	OH	7,8-$(OH)_2$	3.80 ± 0.41
OMe	OMe	H	7,8-$(OH)_2$	13.87 ± 0.92
OMe	OMe	OMe	7,8-$(OH)_2$	18.40 ± 4.98
OH	OH	H	5,7-$(OH)_2$	8.72 ± 0.28
H	OMe	H	5,7-$(OH)_2$	> 3700
OMe	OMe	H	5,7-$(OH)_2$	17.41 ± 1.47
OH	OH	H	6,8-$(OH)_2$	1.64 ± 0.10 (**98b**)
OMe	OMe	H	6,8-$(OH)_2$	106.42 ± 0.51

A combination of the coumarin and thiosemicarbazide scaffolds afforded a series of compounds **99**, which were evaluated for antiglycation activity in the glucose–BSA system.[110] It was demonstrated that, despite the structural modification using the variation of substituents in the aryl group of the carbazide moiety of the molecule, all compounds inhibited the AGE formation to a smaller extent compared to aminoguanidine employed as the reference compound (74.93 ± 1.266 μM) (Table 34).

Table 34. Antiglycation activity of compounds **99**.[110]



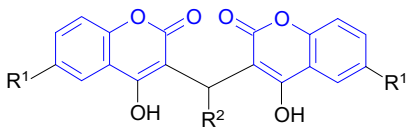
99

R	Inhibition of AGE formation [a] (%)	R	Inhibition of AGE formation [a] (%)
	50.78 ± 1.322		37.12 ± 1.284
	64.27 ± 2.282		53.08 ± 0.520
	39.21 ± 1.283		64.41 ± 1.035
	68.66 ± 2.111		61.81 ± 2.179
	56.61 ± 1.540		56.34 ± 1.779
	62.49 ± 2.076		61.42 ± 1.610
	65.09 ± 2.59		47.22 ± 0.505
	38.91 ± 1.522		64.81 ± 0.899
	51.24 ± 0.945		

[a] M = 100 μM.

Choudhary and co-workers [111] synthesized a representative series of bis-coumarins **100** and evaluated their biological activity. The authors noted that most of compounds did not show statistically significant antiglycation activity, and only some derivatives containing di- or trisubstituted phenolic moieties R^2 exhibited activity in the high micromolar range (IC_{50} = 333.63–919.72 μM). Besides, it was demonstrated that the replacement of a hydrogen atom at the C(6) position by a chlorine or fluorine atom has no significant effect on this kind of activity.

Structure 100

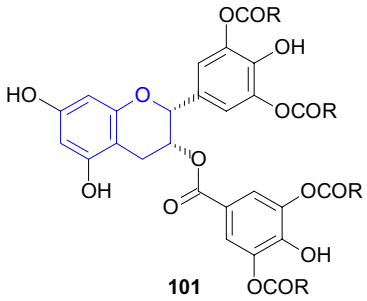


100

R^1 = H, Cl, F;
R^2 = Ar

Another modification of natural benzopyrans, epigallocatechin gallates **101**, involved the acylation of four hydroxyl groups by carboxylic acid containing alkyl chains of different lengths.[112] However, none of the synthesized derivatives showed a stronger suppression of AGE fluorescence compared to aminoguanidine used as the positive control (80% at a concentration of 100 μM) (Table 35).

Table 35. Antiglycation activity of compounds **101**.[112]



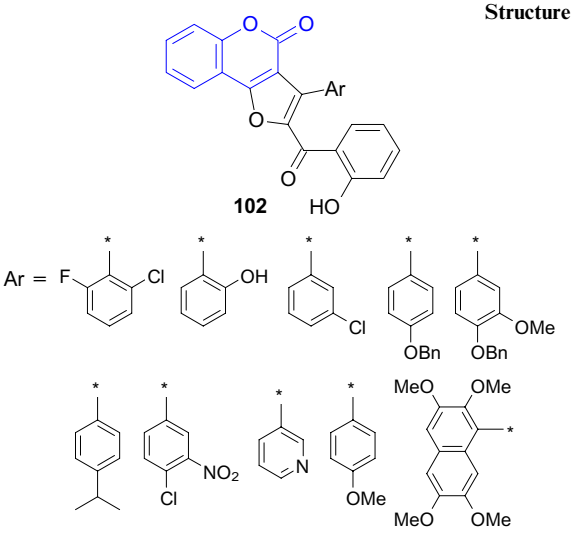
101

R	Inhibition of AGE formation [a] (%)	R	Inhibition of AGE formation [a] (%)
H	64	$(CH_2)_6Me$	73
Me	72	$(CH_2)_{10}Me$	71
Et	66	$(CH_2)_{16}Me$	73
$(CH_2)_4Me$	72	$(CH_2)_4(CH{=}CHCH_2)_6Me$	42

[a] M = 100 μM.

Functionalized furo[3,2-*c*]coumarins **102** did not exhibit significant antiglycation activity, except the tetramethoxynaphthalene derivative (IC_{50} = 364.6 ± 32.8 μM).[113] These data suggest that this class of heterocycles is of no interest as potential compounds capable of inhibiting AGE formation.

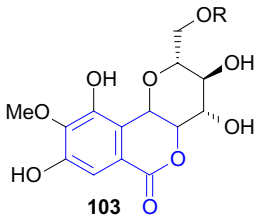
Structure 102



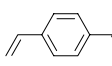
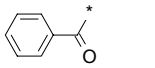
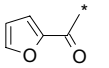
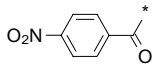
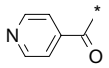
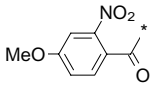
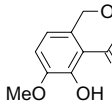
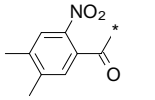
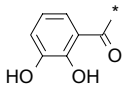
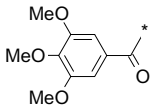
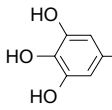
Fused benzopyranone analogues **103**, bergenin derivatives, were described by Kumar *et al.*[114] In this series of heterocycles, nitro derivative **103a** was found to be the most active (IC_{50} = 43.90 ± 12.69 μM). It should be noted that the analogues containing free hydroxyl groups in the benzoyl moiety also exhibited pronounced activity. The methylation of the hydroxyl groups led to the loss of antiglycation activity (Table 36).

It is worth noting that almost all publications dealing with the antiglycation activity of coumarins and benzopyranones described compounds with IC_{50} values in the range of 10–100 μM and in some cases in the low micromolar range (< 10 μM), which is evidence that this scaffold is promising for discovering compounds with antidiabetic

Table 36. Antiglycation activity of compounds **103**.[114]



103

R	IC_{50} ± SEM, μM	R	IC_{50} ± SEM, μM
H	110.47 ± 7.41		NA
	75.69 ± 2.64		NA
	NA		NA
	NA		NA
	43.90 ± 12.69 (**103a**)		93.27 ± 4.23
	NA		83.62 ± 9.23

activity and for the therapy of other AGE-associated diseases. The following structure–activity relationships should be noted (Fig. 5):

— the enhancement of the antiglycation effect is observed in the presence of R^1 = H, Me, Ac, $(CH_2)_2NAlk_2$;

— the substitution of the phenyl moiety in the *para* position by the methoxy group (R^2 = OMe) or in the *meta* position by the nitro group ($R^2 = NO_2$) is a beneficial modification;

— the replacement of the 2(4)-aryl moiety by a hetaryl moiety results in a significant decrease in the antiglycation effect;

— the fusion of the benzopyranone system to other cyclic moieties leads to a decrease in the antiglycation activity.

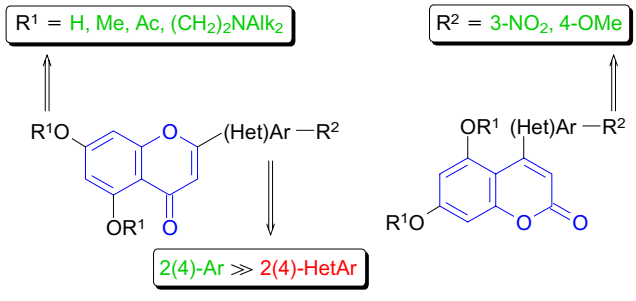
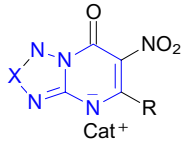


Figure 5. Structure–activity relationship for the benzopyranone scaffold.

2.8. Miscellaneous fused heterocyclic systems

A number of publications concerned with the evaluation of antidiabetic activity of fused heterocycles of different nature, starting with azoloazines and ending with fluoroquinolones. It was demonstrated that the replacement in the triazole ring in a series of 6-nitroazolo[1,5-*a*]pyrimidin-7-ones **104** has a significant effect on the antiglycation activity. Thus, compounds containing the α-furyl moiety exhibited the highest activity (Table 37). It should be noted that the antiglycation activity of water-soluble salts is lower compared to the corresponding NH forms of these heterocycles. Besides, the replacement of the 1,2,4-triazole ring by the tetrazole one led to a threefold decrease in antiglycation activity.[115]

Table 37. Antiglycation activity of compounds **104**.[115]



104

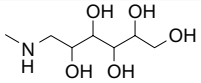
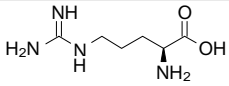
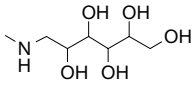
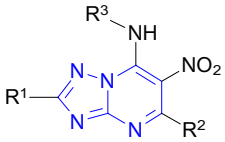
X	R	Cat$^+$	$IC_{50} \pm SEM$, μM
CH	Me	H	136.72
CH	Me	Na	161.28
CMe	Me	H	202.53
CSMe	H	H	111.99
CSMe	H		118.29
CCF_3	Me	H	117.17
C-(fur-2-yl)	H	H	50.35
C-(fur-2-yl)	H		120.04
C-(fur-2-yl)	H		102.30
C-(pyridin-3-yl)	Me	H	202.44
N	Me	H	450.9

Table 38. Antiglycation activity of compounds **105**.[115]



105

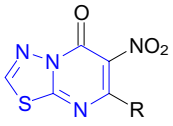
R^1	R^2	R^3	$IC_{50} \pm SEM$, μM
H	Me	Pr^i	580.66
H	Me	$AcO(CH_2)_2$	179.56
CF_3	Me	Pr^i	690.75
CF_3	Me	Bu^n	NA
CF_3	H	Bu^n	NA
Fur-2-yl	H	Bu^n	NA

On the contrary, 2*H*-derivatives were found to be the most active in the series of hydrophobic 7-alkylamino-6-nitrotriazolo[1,5-*a*]pyrimidines **105**, whereas the furyl-containing heterocycle did not show the statistically significant antiglycation effect (Table 38). However, hydrophilic triazolo[1,5-*a*]pyrimidines **104** are generally more prone to inhibit glycation compared to their hydrophobic analogues **105**.

The inverse relationship was observed in the series of 5-alkylamino-6-nitro-1,3,4-thiadiazolo[3,2-*a*]pyrimidines **106**. Thus, the antiglycation activity increases with increasing hydrophobicity of the alkyl group, the lowest IC_{50} values were determined for the phenyl-containing heterocycles (Table 39).[116] However, the highest activity in this series was found previously[115] for 5-hydroxy-6-nitrothiadiazolopyrimidin-7-one **106a**.

The antiglycation activity of azolo-1,2,4-triazine derivatives **107** and **108** was evaluated in the study.[117] Based on these data, structure–activity relationships were established. Thus, triazolo-1,2,4-triazine scaffold **107** (Table 40) has a lower potential in searching for compounds inhibiting AGE formation compared to the corresponding pyrazolo-1,2,4-triazines **108** (Table 41). Besides, the replacement of a hydrogen atom in the triazole ring by other moieties leads to a decrease in the antiglycation effect.

Table 39. Antiglycation activity of compounds **106**.[116]



106

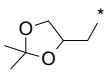
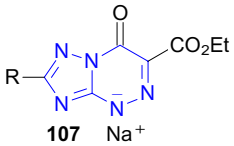
R	Inhibition of AGE formation (%) (M = 100 μM)	IC_{50}, μM	R	Inhibition of AGE formation (%) (M = 100 μM)	IC_{50}, μM
OH	ND	111.99 (**106a**)	$NH(CH_2)_4OAc$	11.5 ± 2.4	NA
Bu^nNH	32.1 ± 8.7	204.1	$NH(CH_2)_2OH$	29.5 ± 2.8	NA
Bu^iNH	23.1 ± 5.8	289.8	$NH(CH_2)_3OH$	16.1 ± 2.1	NA
Bu^tNH	21.3 ± 2.7	181.2	$NH(CH_2)_4OH$	26.1 ± 0.7	NA
Pr^nNH	14.9 ± 7.5	NA	$NH(CH_2)_2C_6H_4$-4-Cl	48.8 ± 3.6	134.4
Pr^iNH	30.0 ± 0.5	325.1	$NH(CH_2)_2C_6H_4$-4-OH	43.8 ± 2.5	166.8
$NH(CH_2)_2OAc$	44.8 ± 1.0	NA	$NHCH_2CH(OH)CH_2OH$	10.3 ± 6.1	NA
$NH(CH_2)_3OAc$	12.5 ± 2.0	NA		42.1 ± 0.7	208.7

Table 40. Antiglycation activity of compounds **107**.[117]



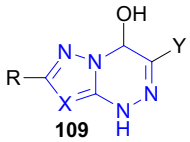
107

R	Inhibition of AGE formation (%)	
	M = 1000 μM	M = 100 μM
H	66.92 ± 2.67	17.66 ± 5.30
Me	16.65 ± 7.01	8.51 ± 5.69
SMe	20.12 ± 5.41	20.62 ± 7.39
SEt	24.21 ± 6.91	4.38 ± 7.05
SPr^n	28.57 ± 2.61	21.49 ± 4.81
SPr^i	31.69 ± 7.05	13.48 ± 4.35
CO_2Et	29.96 ± 11.56	7.29 ± 9.80

On the other hand, pyrazolo-1,2,4-triazine **108** containing the ethoxycarbonyl-substituted pyrazole ring exhibits higher antiglycation activity compared to the related compound bearing the carboxyl substituent (see Table 41). Similar pattern was observed when varying the substituent on the triazine moiety. Thus, the replacement of the ethoxycarbonyl group by the nitro, cyano or amino group led to a decrease in the activity. The analysis of these data revealed a number of compounds with activity in the mid-micromolar range. Extended *in vivo* studies of compound **108a** demonstrated its ability to retard the process of cataractogenesis due to a decrease in the AGE level in ocular lenses of animals.[118]

The evaluation of the activity of 1,4-dihiydroazolo-1,2,4-triazines **109** demonstrated that, in the presence of the 1,2,4-triazole moiety, compounds containing a cyano rather than a nitro group as the substituent Y exhibit higher activity (Table 42). However, the replacement of the 1,2,4-triazole ring by 4-ethoxycarbonylpyrazole gives nitro derivative **109b**, the antiglycation activity of which is more than two times higher compared to that of nitrile analogue **109a**.[119]

Table 42. Antiglycation activity of compounds **109**.[119]



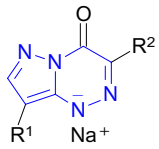
109

X	Y	R	Inhibition of AGE formation (%) (M = 1000 μM)
N	CN	H	71.6 ± 2
N	CN	Me	58.7 ± 2.1
N	CN	SMe	37.9 ± 3.3
C–CO_2Et	CN	H	30.1 ± 2.5 (**109a**)
N	NO_2	$SCH_2C{\equiv}CH$	38.5 ± 0.7
N	NO_2	H	40.4 ± 2.0
N	NO_2	Me	33.6 ± 5.9
N	NO_2	SMe	23.0 ± 3.5
C–CO_2Et	NO_2	H	63.5 ± 0.4 (**109b**)
N	NO_2	Thien-2-yl	55.6 ± 2.5

In the series of guanidyl-substituted azolotetrazines **110**, many compounds show the antiglycation effect higher than that of aminoguanidine hydrochloride used as the reference compound (Table 43). Particular mention should be made of 3-dodecylthio-6-guanidino[1,2,4]triazolo[4,3-*b*][1,2,4,5]-tetrazine **110a** exhibiting antiglycation activity in the mid-micromolar range (IC_{50} = 38.8 μM).[120]

Spasov *et al.*[121] demonstrated that purines **111** and related thiazolo[2,3-*f*]purines **112**, taken at a concentration of 100–1000 μM, either do not show the statistically sig-

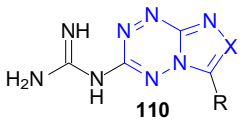
Table 41. Antiglycation activity of compounds **108**.[117]



108

R^1	R^2	Inhibition of AGE formation (%)		IC_{50} ± SEM, μM
		M = 1000 μM	M = 100 μM	
CO_2Et	CO_2Et	88.76 ± 0.92	65.33 ± 2.00	53.96 (**108a**)
CO_2Na	CO_2Et	86.45 ± 0.64	59.85 ± 3.53	96.14
CN	CO_2Et	30.65 ± 2.92	−27.27 ± 5.31	NA
CO_2Et	NO_2	79.76 ± 4.23	28.30 ± 9.28	338.55
CN	NO_2	50.41 ± 10.86	−14.98 ± 90.82	NA
C(=NOH)NH_2	NO_2	76.05 ± 1.44	25.08 ± 3.30	NA
CO_2Et	CN	86.48 ± 0.25	56.60 ± 2.58	116.77
CO_2Na	CN	91.07 ± 0.17	58.90 ± 1.48	122.12
CO_2Et	C(=NOH)NH_2	91.10 ± 0.33	58.76 ± 2.52	70.58
CO_2Na	C(=NOH)NH_2	91.57 ± 0.18	57.45 ± 2.25	158.81
CO_2Et	$CONHBu^t$	89.26 ± 0.16	62.00 ± 2.08	48.13 (**108b**)
CO_2Na	$CONHBu^t$	86.41 ± 0.27	56.18 ± 2.74	130.80
CO_2Et	NH_2	−22.01 ± 11.12	−14.90 ± 2.98	NA
CO_2Na	CO_2Na	37.91 ± 4.81	14.15 ± 4.66	NA

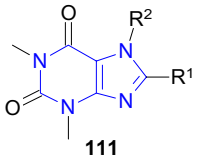
Table 43. Antiglycation activity of compounds **110**.[120]



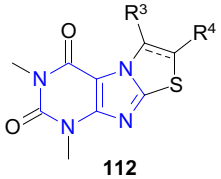
110

X	R	Inhibition of AGE formation (%)		$IC_{50} \pm SEM$, μM
		M = 1000 μM	M = 100 μM	
CH	H	43.53 ± 3.21	16.51 ± 2.71	NA
CH	SPr^i	66.30 ± 2.26	28.48 ± 3.32	508.0
CH	$SC_{12}H_{25}$-n	77.86 ± 0.95	76.18 ± 0.65	NA
N	H	55.02 ± 3.07	8.24 ± 5.45	NA
N	SPr^i	73.81 ± 1.66	18.25 ± 3.98	287.1
N	$SC_{12}H_{25}$-n	69.34 ± 1.36	48.37 ± 0.88	38.8 (**110a**)
N	NH_2	50.69 ± 0.53	−1.60 ± 8.86	NA

Structures 111, 112



111



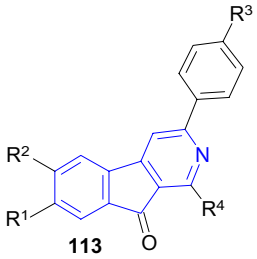
112

nificant antiglycation effect or, on the contrary, promote AGE formation.

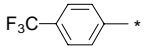
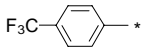
Other heterocyclic scaffolds, *e.g.*, 9*H*-indeno[2,1-*c*]pyridin-9-ones **113**, were also evaluated for antiglycation activity.[122] In this series, several structures demonstrated the ability to bind AGEs produced in the MGO–BSA system but only at a concentration of 1000 μM (Table 44).

Hamdan *et al.*[123] evaluated the antiglycation activity of various fluoroquinolones and revealed structure–activity relationships. The authors reported that 8-aminofluoroquinolones **115** and the corresponding fused 1,2,3-triazole analogues **116** are more active than starting 8-nitro derivatives **114** due apparently to their ability to chelate metal

Table 44. Antiglycation activity of compounds **113**.[122]



113

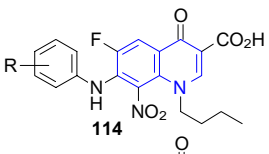
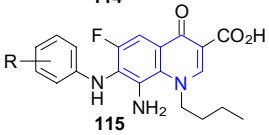
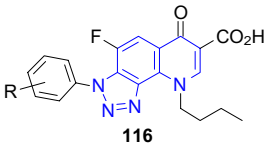
R^1	R^2	R^3	R^4	Inhibition of AGE formation (%) (M = 1000 μM)
Br	H	OMe		94.95
OMe	OMe	H		52.55
Br	H	Me		55.09

ions, which promote the Maillard reaction (Table 45). Besides, it was found that the substituent R on the side phenyl ring affects the antiglycation activity. Thus, the replacement of the methyl moiety by halogen atoms facilitates the decrease in IC_{50} values. It is worth noting that in the series of fluoroquinolones, compounds **115a**,**b** and **116c** exhibit activity in the nanomolar range.

A similar structure–activity relationship was observed in the series of N(1)-*cyclo*-propylfluoroquinolones **117**–**119** containing the hexyl substituent on the phenyl ring.[124] Compound **119** based on the 1,2,3-triazole scaffold proved to be the most active, C(8)-amino derivative **118** was less active and C(8)-nitro-substituted heterocycle **117** showed the lowest antiglycation activity in this series. Nevertheless, all three fluoroquinolones have the half-maximal inhibitory concentration in the low micromolar range.

A comparison of the activity of the *cis* and *trans* isomers of 2,3,5-triarylpyrrolo[3,4-*d*]isoxazoles **120** and **121** demonstrated that *cis* derivatives **120** exhibit higher antiglycation activity compared to their *trans* analogues **121**

Table 45. Antiglycation activity of compounds **114**–**116**.[123]

Scaffold	$IC_{50} \pm SEM$, μM					
	R					
	2-Me	3-Me	4-Me	4-F	4-Cl	4-Br
 **114**	461.1 ± 41.5	2.9 ± 0.2	677.3 ± 60.96	6.1 ± 0.6	23.5 ± 2.1	6.3 ± 0.6
 **115**	23.2 ± 2.1	31.3 ± 2.8	37.04 ± 3.3	0.15 ± 0.01 (**115a**)	4 ± 0.4	0.4 ± 0.03
 **116**	14.1 ± 1.3	207.7 ± 18.7	355 ± 32	11.2 ± 1.01	0.05 ± 0.00 (**116c**)	126.9 ± 11.4

Structures 117 – 119

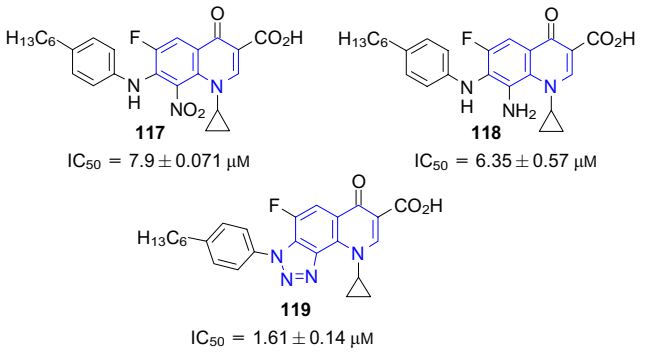
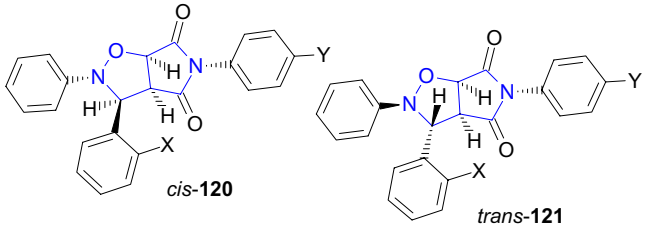


Table 46. Antiglycation activity of compounds **120** and **121**.[25]



Configuration	X	Y	$IC_{50} \pm SEM$, μM	X	Y	$IC_{50} \pm SEM$, μM
cis	Cl	H	7.40 ± 1.30	OH	H	25.90 ± 1.60
trans			30.91 ± 2.20			64.77 ± 2.30
cis	Cl	Me	7.18 ± 1.45	OH	Me	18.76 ± 1.82
trans			23.92 ± 1.92			75.00 ± 2.00
cis	Cl	OMe	8.63 ± 1.61	OH	OMe	26.60 ± 2.11
trans			24.17 ± 1.80			90.10 ± 1.80
cis	Cl	CO_2H	33.05 ± 2.11	OH	CO_2H	24.40 ± 1.91
trans			126.67 ± 2.31			63.90 ± 2.21

(Table 46).[125] Besides, the presence of a chlorine atom on the C(3)-aryl moiety is preferable over the hydroxy group.

Therefore, many fused heterocyclic systems, primarily compounds of the azoloazine series, have the antiglycation activity in the mid-micromolar range. On the contrary, fused purines and thiazolo[2,3-*f*]purines produced no antiglycation effect. Fluoroquinolones **114** – **116** are the most effective inhibitors of AGE formation. Lead compound **116c** showed the IC_{50} value in the nanomolar range. *cis*-Pyrrolo[3,4-*d*]isoxazoles **120** also exhibit high antiglycation activity.

3. Conclusion

An analysis of modern scientific publications dealing with the discovery of small synthetic molecules with antiglycation activity, *i.e.*, molecules capable of inhibiting AGE formation, demonstrated that various classes of compounds have attracted attention of researchers, and it is difficult to present these compounds in a unique classification. Figure 6 shows selected lead compounds, the half-maximal inhibitory concentrations for which are in the low micromolar range or even in the nanomolar range.

Despite significant differences in the structures of these compounds, most of depicted molecules contain the phenyl moiety as the substituent. Therefore, the structural optimi-

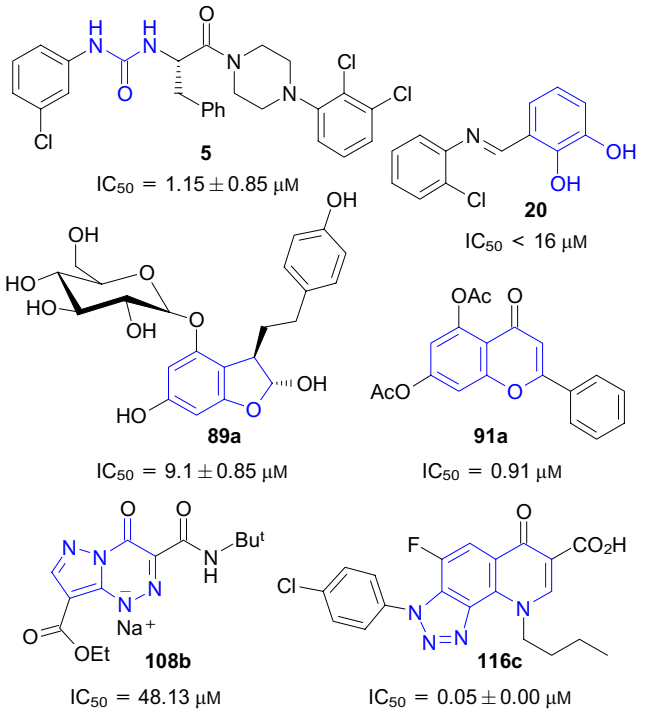


Figure 6. Most promising small synthetic molecules with antiglycation activity.

zation is one of distinguishing features of the evaluation of the inhibitory activity against AGE formation and other diabetes-associated targets. In many cases, this structural optimization involves only the variation of the substituents R^1/R^2 on the phenyl rings bound to the major scaffold either directly or through a linker. It is worth noting that the use of a hydroxyl or nitro group and halogen atoms as the substituents R^1/R^2 leads to the enhancement of antiglycation activity; on the contrary, alkyl, trifluoromethyl and sterically hindered groups cause a decrease in the activity. Besides, the replacement of phenyl groups by hetaryl or nonaromatic moieties often leads to the loss of antiglycation activity. A combination of several scaffolds in one molecule also does not give rise to a synergistic effect, resulting in the ability of such chimeric compounds to inhibit AGE formation at the level characteristic of each particular scaffold but not higher.[92, 110, 120]

Considerable prospects are associated with heterocyclic compounds, primarily with oxygen- and nitrogen-containing systems. Advantages of these molecules are not only the antiglycation activity in the low micromolar range but also considerable possibilities of structural optimization, enhanced metabolic stability compared to (thio)ureas and the ability to inhibit AGEs in systems *in vivo*.[118] Besides, the mechanism of antiglycation of nitrogen-containing heterocycles apparently differs from that for other scaffolds because the inhibitory ability of the latter against AGE formation is often related to the presence of halogen atoms or hydroxyl groups as substituents. In heterocyclic compounds, the presence of these functional groups is not a necessary condition for the manifestation of antiglycation activity.

Therefore, a promising line of research is the discovery of new compounds with antiglycation activity in the nanomolar range *via* the screening of new nitrogen- and oxygen-

containing heterocyclic systems, primarily azoloazines, fluoroquinolones, benzopyranones and benzofurans. The reasonable structural modification of these systems, which has not been studied previously and which potentially enhances the antiglycation activity, is based on the introduction of polyphenol moieties or halogen-substituted phenyl groups. Another promising class is represented by (thio)ureas containing phenyl groups with halogen atoms or hydroxyl groups; however, as opposed to heterocyclic systems, the *in vivo* experimental data on the possibility of inhibition of AGE formations are lacking.

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4. List of abbreviations and designations

AGEs — advanced glycation end products;
AMO — acetone monooxygenase;
Bn — benzyl;
BSA — bovine serum albumin;
DM — diabetes mellitus;
HbA1c — glycated haemoglobin;
IC_{50} — half-maximal inhibitory concentration;
MGO — methylglyoxal;
M — molar concentration;
NA — not active;
ND — not determined;
RAGE — receptor for advanced glycation end products;
SEM — standard error of the mean;
SSAO — semicarbazide-sensitive amine oxidase.

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