Drugs of the Future 1999, 24(11): 1241-1248

CCC: 0377-8282/99

Review Article

Thioglycoside antithrombotic agents

Gabriella Szabó, Éva Bozó, Éva Barabás, Rita Kedves, Katalin Csomor[1] and János Kuszmann*

*Institute for Drug Research, P.O.B. 82, 1325 Budapest and [1]Gedeon Richter Chemical Works Ltd. P.O.B. 27, 1475 Budapest, Hungary. *Correspondence*

CONTENTS

Introduction

Despite the fact that the biosynthesis of the glycosaminoglycan (GAG) components of proteoglycans is not yet fully understood, heparin, belonging to this type of sulfated polysaccharides, has been the antithrombotic of choice for over half a century (1). The most serious drawback to heparin therapy is that it cannot be administered orally. Heparin induces thrombocytopenia with hemorrhagic complications or thrombocytopenia and thrombosis. Patients with thrombocytopenia and thrombosis are at high risk for developing arterial or venous thrombosis, resulting in loss of limb or life in > 30% of those patients with heparin antibodies (2, 3). Since other sulfated GAG molecules produced in normal cells, such as dermatan sulfate, chondroitin sulfate and heparan sulfate, possess *in vivo* antithrombotic activity (4, 5), increasing their concentration in the circulating blood seemed to be a promising alternative for the treatment of thrombosis. This type of research was based on the observation of Okayama *et al.* (6) who demonstrated in 1973 that in slices of embryonic chick cartilage, simple aromatic β-D-xylosides such as *p*-nitrophenyl β-D-xylopyranoside can act as exogenous substrate and compete effectively with the xylosylserine core of the endogenous protein in accepting the transfer of galactose units from UDP-galactose, the key step in the carbohydrate chain elongation in the biosynthesis of proteochondroitin sulfate. This finding was confirmed 1 year later by Schwartz *et al.* (7) who detected the same reaction in different cell and tissue cultures. These results indicated that certain types of tissue cells contain the enzymatic machinery necessary for the synthesis of chondroitin sulfate which is normally dormant but can be activated by certain β-D-xylopyranosides. In 1977, Schwartz postulated (8) that these compounds act as initiators of chondroitin sulfate chains at the second glycosyl transfer step, thereby eliminating the need for both the core protein and xylosyltransferase.

Later, Lugemwa and Esko (9) showed that the structure of sulfated GAG molecules depends highly on the aglycon part of the β-D-xylopyranosides used as primers. While the synthesis of chondroitin sulfate was stimulated by a broad variety of aglycons (methyl, *n*-octyl, *p*-nitrophenyl, 4-methylumbelliferyl, farnesyl, cholesteryl and estradiol), only heparan sulfate was effectively primed by the estradiol xyloside. In addition, this xyloside simultaneously inhibited the formation of endogenous heparan sulfate proteoglycans. To find an explanation for these phenomena, one must assume that estradiol xyloside can act not only as a primer initiating the synthesis of certain exogenous GAGs but also as a specific enzyme inhibitor, blocking the synthesis of the endogenous counterparts (10). In this respect, it should be mentioned, that under normal conditions, core protein expression, the extent of xylosylation, or the flux of core protein substrates passing from the endoplasmic reticulum through the Golgi apparatus are a limiting factor in the synthesis of GAG and their concentration in the circulation. On the other hand, flooding cells with high concentrations of β-D-xylopyranosides apparently bypass the restriction and provide a large number of primers for chain elongation. Thus, the exogenous GAGs that are formed are immediately excreted into the blood and provide a relatively high concentration of molecules with potential antithrombotic activity.

Chondroitin sulfate and heparan sulfate have identical core regions, *i.e.*, GlcAβ1-3Galβ1-3Gα1-4Xylβ1-aglycon, and differ only in the amino sugar residue attached to the terminal 4GlcAβ1 residue during the further chain elongation steps (GlcNAcα1 for heparan sulfates and GalNAcβ1 for chondroitin sulfate). Accordingly, the observed substrate specificity means that the difference in the aglycon moiety, which is separated from the site of elongation by 4 carbohydrate units, still directs the attachment of the next amino sugar moiety. This was proven in 1997 by Fritz *et al.* (11) for the core tetrasaccharide containing

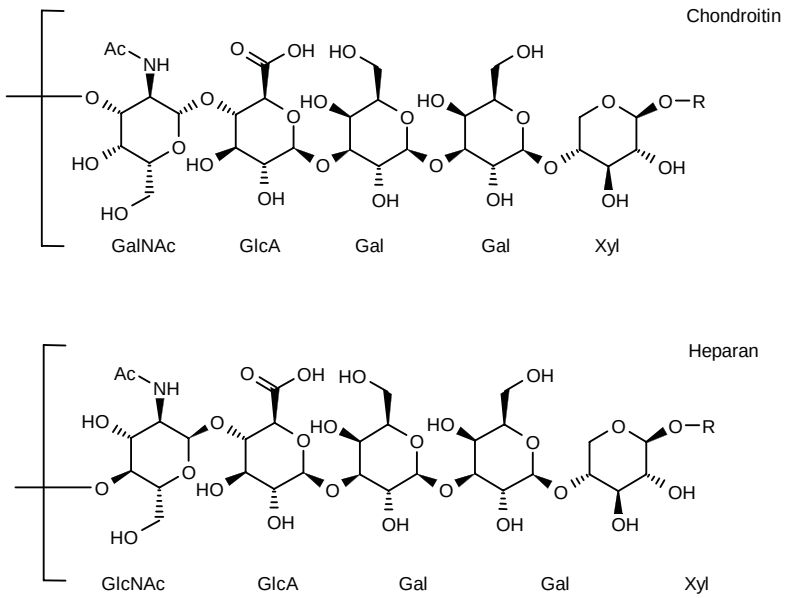


Fig. 1. The core region of chondroitin sulfate and heparan sulfate.

2-naphthalenemethanyl β-D-xylopyranoside at the reducing end as this glycoside was directly recognized by α-*N*-glucosaminotransferase, responsible for the chain elongation at the nonreducing end of the tetrasaccharide (Fig. 1).

Based on these facts, researchers at Laboratoires Fournier initiated an ambitious program to search for orally active antithrombotics. In their first attempt, they established structure-activity relationships (SAR) for different glycosides using D-glucose, D-galactose, *N*-Ac-D-glucosamine, D-mannose, D-xylose, D-glucuronic acid, L-fucose as well as two disaccharides, maltose and lactose, as carbohydrate carriers and substituted benzophenone, benzhydrol and benzhydryl as aglycon (12). For evaluation of the antithrombotic activity, the Wessler stasis type model of venous thrombosis was applied in rats (13). The biological data obtained with different *O*-glycosides demonstrated that the β-D-xylopyranosides possessed the highest activity. However, these compounds proved to be inactive in rabbits which is the species frequently used in antithrombotic assays. This was thought to be due to the fact that rabbits, in contrast to rats, have very efficient glycosidases which rapidly cleave the glycosidic bonds thus inactivating the molecule. Since glycosides of thio sugars are usually much more resistant towards glycosidases (14), both the endocyclic and exocyclic oxygen of the xylopyranose moiety was exchanged alternatively or simultaneously by sulfur (15). The data depicted in Figure 2 are in accordance with the expectation that the activity of the xylopyranosides could be substantially increased by exchanging one or both oxygen atoms with sulfur and that the dithio derivative was already active in rabbits.

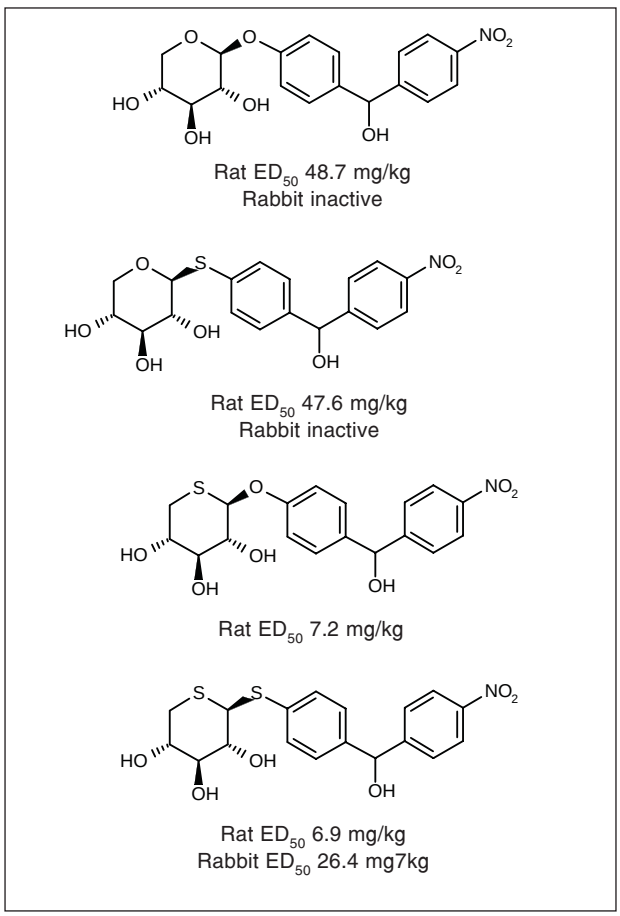
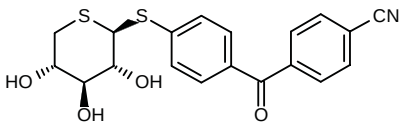


Fig. 2. Oral antithrombotic activities of -O,O; -O,S-; -S,O-; and -S,S- glucosides in the Wessler model.



Rat ED_{50} 8.5 mg/kg
Rabbit ED_{50} 36.0 mg/kg

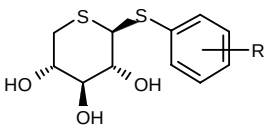
Fig. 3. Oral antithrombotic activity of naroparcil.

The antithrombotic effect of the dithioxylosides could be further increased by alteration of the aglycon and finally, the 4-(4-cyanobenzoyl)phenyl 1,5-dithio-β-D-xylopyranoside was submitted under the name naroparcil to clinical investigation (15, 16) (Fig. 3).

It is noteworthy that the antithrombotic effect of these derivatives appears only hours after administration (usually 2 h after i.v. and 4 h after oral administration), suggesting that some metabolic processing of these compounds is required. Furthermore, these compounds have no effect in classic *in vitro* coagulation tests such as the activated partial thromboplastin time or thrombin time assays and the sensitized thrombin time assay was only affected at very high doses of 400 mg/kg, exceeding ~ 50 times the ED_{50} dose (13). As naroparcil was well tolerated in cynomolgus monkeys up to 2000 mg/kg p.o. for 28 days, it was submitted to clinical trials but failed due to its extensive metabolization. As the aglycon was the main site of metabolism, a number of simpler structures, *i.e.*, substituted thiophenol xylosides, were synthesized and investigated (15).

As can be seen from Table I, electron withdrawing substituents substantially increased the activity of the unsubstituted derivative (R = H). Accordingly, the most active compound, beciparcil, was submitted to clinical investigation. However, the development of this compound was also terminated since human volunteers experienced mild rashes and itching (Table I).

Table I: Antithrombotic activity of substituted phenyl 1,5-dithio-β-D-xylopyranosides in rat venous thrombosis model (Wessler-using factor Xa) 4 h after oral administration (15).



R	Activity %*
4-CN (beciparcil)	90
3-CN	79
2-CN	89
4-NO_2	67
4-Me	37
4-OMe	9.5
H	11
4-Cl	6

*Inhibition at 12.5 mg/kg.

Our institute has been involved in antithrombotic research for decades, and in the synthesis and evaluation of peptide derivatives in particular. This line of investigation led to the discovery of the highly active tripeptide aldehyde, GYKI-14766 (efegatran) (17, 18). As this compound had only moderate oral bioavailability, further research was centered mainly on orally active derivatives. In order to extend this project to nonpeptide structures, we broadened the SAR investigations in the field of the thioglycosides, initiated by Fournier. Actually, we pursued three lines in our investigation: 1) the influence of the change of the *p*-substituent of the aglycon in beciparcil; 2) the role of the individual hydroxyl groups of the xylopyranose residue; and 3) the role of the structure and stereochemistry of the carbohydrate moiety.

Beciparcil analogs differing in substitution of the aglycon

The Pescador model was chosen to examine the biological activity of the new derivatives (19). This model is a quantitative venous thrombosis model with stasis based on vascular lesion in rats and differs from the Wessler venous model in the provocation of the thrombus. In this rat model, thrombus formation was induced with stasis and human serum. According to our earlier experience, the Pescador model is reliable and reproducible and gives satisfying dose-activity relationships although the results are often different from those in which other types of provocation are used. Consequently, the activities of the different compounds obtained using different test methods should not be compared as this would result in misleading conclusions as far as SAR are concerned.

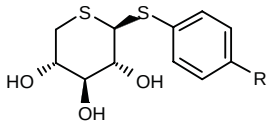
As shown in Table II, the activity of the reference compound beciparcil was only 25 mg/kg in this model (20, 21). According to another study (15), its ED_{50} value was 8.5 determined by the Wessler model using factor Xa. However, this activity could be substantially increased by converting the cyano group into carboxylic acid derivatives. Among these new compounds, the methylthioimino derivative showed the highest activity and was chosen for further biological investigations.

Beciparcil analogs differing in substitution of the xylopyranose residue

To investigate the role of the individual hydroxy groups of the xylopyranose moiety on biological activity, we exchanged them for hydrogen or azide. First of all, the 2-OH group, as any group vicinal to the anomeric substituent, may substantially influence the biological activity (see RNA → DNA) (Table III).

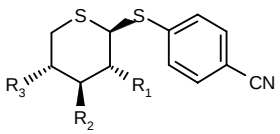
According to the data shown in Table III (20-25), the corresponding 2-deoxy derivative proved to be ~3.5-fold

Table II: Antithrombotic activity of substituted phenyl 1,5-dithio-β-D-xylopyranosides in rat venous thrombosis model (Pescador) 3 h after oral administration (20).



R	ED_{50} (mg/kg)
CN (beciparcil)	25
C(=NH)OMe	10
$CSNH_2$	5
C(=NH)SMe.HI	1.5
$C(=NH)NH_2$.AcOH	5
$C(=NH)NHNH_2$	2

Table III: Antithrombotic activity of 4-cyanophenyl 1,5-dithio-β-D-xylopyranosides in which the individual OH groups of the sugar residue are exchanged by H or N_3 groups, in rat venous thrombosis model (Pescador) 3 h after oral administration.

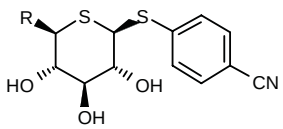


R_1	R_2	R_3	ED_{50} (mg/kg)	Ref.
OH	OH	OH	25	20
H	OH	OH	7	22
H	H	OH	3	23
N_3	OH	OH	7	24
OH	N_3	OH	10	24
OH	NH_2	OH	13	24
OH	NHAc	OH	50	24
OH	OH	N_3	6.5	25

as active as beciparcil and the 2,3-dideoxy derivative was even more active. Generally, the role of the hydroxy groups in carbohydrate derivatives is important because of the formation of hydrogen bridges ensuring water solubility as well as their interaction with the active sites of the corresponding receptor molecules. On the other hand, 2-deoxy derivatives are usually much more acid-sensitive as compared to their 2-OH analogs (26), and the presence of the 2-OH group may influence the chemical reactivity of the glycosidic bond by neighboring group participation.

For this reason, synthesis of the corresponding 2-azido analog was decided, as the OH → N_3 change would eliminate the possibility of hydrogen bond formation without altering the acid sensitivity of the glycosidic bond. However, as documented in the case of the synthesis of active anti-HIV nucleosides (27, 28), such a substitution may cause a dramatic shift in the properties of

Table IV: Antithrombotic activity of 4-cyanophenyl 1,5-dithio-β-D-hexopyranosides in rat venous thrombosis model (Pescador) 3 h after oral administration.



R	ED_{50} (mg/kg)	Ref.
H	25	20
CH_2OH	7	29
CH_3	12	29
CH_2=	15	29

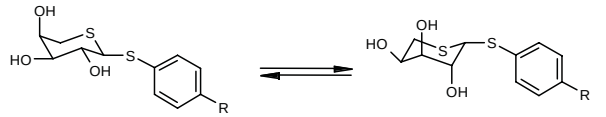
biologically active carbohydrate derivatives. The antithrombotic activity of the 2-azido derivative equaled that of the 2-deoxy analog. Consequently, the hydrogen bond forming capacity of the 2-OH group was not essential for this activity. The same holds true for the 3-OH group as its exchange by H or by the N_3 group increased the activity of beciparcil to about the same extent. While the activity was essentially unchanged by the reduction of the 3-azide to an amino group, acetylation of the latter led to a substantial loss in activity. Exchange of the 4-OH group by azide also had a beneficial influence on activity. These data led to the rather surprising conclusion that none of the OH groups of the 5-thio-D-xylopyranose moiety had a particular influence on the antithrombotic activity of the corresponding thioglycosides.

Thioglycosides containing carbohydrate moieties differing in structure from β-D-xylopyranose

In further attempts, we investigated the role of the length of the carbohydrate skeleton, that is, tested the corresponding 5-thio-hexosides. For this reason, the corresponding 5-thio-D-gluco derivatives were synthesized because D-glucose has essentially the same configuration as D-xylose and differs only at the substitution at C-5 (CH_2OH instead of H).

As seen in Table IV (20, 29), the D-gluco analog was again ~3.5 times as active as beciparcil but, when the terminal CH_2OH group was reduced or the corresponding OH group was eliminated via formation of a double bond, the activity dropped significantly. This data was in contrast to a report Bellamy *et al.* (12) which stated that the D-*xylo* configuration of the carbohydrate moiety is essential for the antithrombotic activity. This assumption was based on data obtained from normal glycosides, in which both the endocyclic and the exocyclic oxygens were present. However, the exchange of these two atoms to sulfur essentially alter the properties of the corresponding analogs including the chemical reactivity, structural parameters, conformational flexibility and biological properties. Furthermore, the fact that

Table V: Antithrombotic activity of 4-cyano- and 4-nitrophenyl 1,5-dithio-D-and L-arabinopyranosides in rat venous thrombosis model (Pescador) 3 h after oral administration (30).*



Structure	R	ED_{50} (mg/kg)
α-L	CN	15
β-L	CN	5
α-L	NO_2	2
β-L	NO_2	1.5
α-D	CN	1
β-D	CN	3.5
α-D	NO_2	3.5
β-D	NO_2	3.5

*The structures are given for the L-isomers.

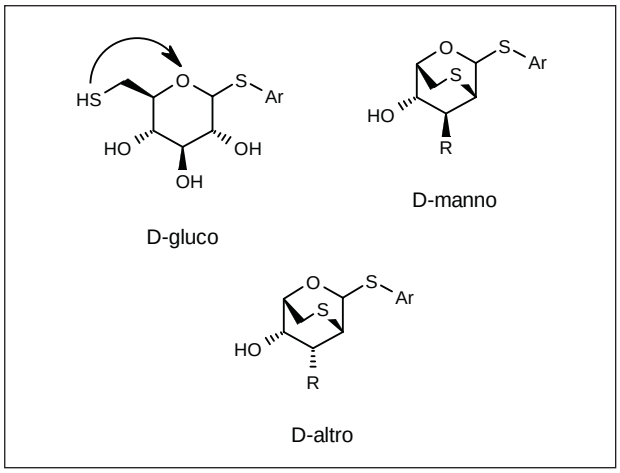


Fig. 4. Transformation of the 6-thio-D-gluco derivatives into 2,6-anhydro-D-manno and D-altro derivatives.

thioglycosides are usually not only more resistant towards enzymatic hydrolysis but can also act as glycosidase inhibitors (12) led to the following hypothesis. It was demonstrated that certain xylosides inhibit the synthesis of endogenous GAG molecules (9) in which a transgalactosidase (8) is involved. Accordingly, it could be presumed that these thioxylosides exert their antithrombotic activity by selectively inhibiting this enzyme. That means that the corresponding 5-thio-D-galactosides should also possess antithrombotic activity. Since the synthesis of 5-thio-D-galactose would be too demanding, the analogous 5-thio-pentose thioglycosides were synthesized. First, the corresponding thioglycosides of 5-thio-L-arabinose were synthesized as L-arabinopyranose, differing from D-galactopyranose only in the substitution at C-5 (H instead of a CH_2OH group).

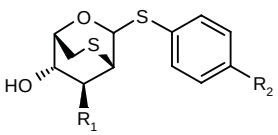
As shown in Table V (30), not only the β-anomers but also the α-pyranosides were more active than beciparcil, and among the L-isomers, the 4-nitrophenyl 1,5-dithio-β-L-arabinopyranoside proved to be the most active. This seemed to be in accordance with the hypothesis that these derivatives may inactivate a certain galactosyltransferase which would enhance the synthesis of the endogenous GAGs. However, the synthesis and investigation of the corresponding D-isomers disproved this idea since the 4-cyanophenyl 1,5-dithio-β-D-arabinopyranoside was even more active (25 times as active as beciparcil) and both anomers of the 4-nitrophenyl analog showed similar ED_{50} values (3.5 mg/kg). It is highly unlikely that both anomers of both antipodes could act with similar efficacy on the same substrate. Nevertheless, it should be mentioned that the 5-thio-arabinopyranosides differ significantly in their conformational mobility from the corresponding 5-thio-xylopyranosides, as the latter entirely occupy one stable conformation ($^4C_1$) in solution, while the former is present in a conformational equilibrium ($^4C_1 = {}_4C^1$).

Finally, we investigated the role of the endocyclic sulfur atom in the carbohydrate moiety in order to synthesize derivatives in which the intermolecular thioether bridge is not a part of the glycosidic system. Theoretically, such compounds can be derived from 6-thio-D-glucopyranosides by closing a 2,6-anhydro bridge which would lead, along with inversion of configuration at C-2, to the corresponding 2,6-thioanhydro-D-mannopyranosides (Fig. 4). The 3-OH group of these derivatives can be exchanged by an azido group or it can be inverted to afford the D-altro configuration.

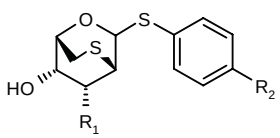
The data in Table VI (31) illustrate that both anomers of the corresponding 4-cyanophenyl thioglycosides were isolated and showed equally strong antithrombotic activity. In this overbridged system, the pyranose ring adopts a boat conformation and the steric arrangement of the anomeric center cannot be compared directly to that of 5-thio-xylopyranosides. Nevertheless, the substitution of the endocyclic sulfur atom by a thioether bridge seems to satisfy the SAR requirements. On the other hand, the transformation of the *p*-substituent of the aglycon into other derivatives, which enhanced the activity in the case of the beciparcil analogs, had the opposite effect in these types of compounds. The same holds for the substitution of the 3-OH group by azide and the inversion of the configuration at C-3 (manno altro).

It is very difficult to draw any definite SAR relationship from the above data, which raises the question as to whether all of these different compounds exert their antithrombotic activity via the same biological pathway. A further finding which strengthens this hypothesis is the fact that different *in vivo* methods result in divergent SARs which can be explained by assuming that the individual methods measure distinct factors playing different roles in the very complex biological pathways involved in thrombus formation (32). Taking into consideration these possibilities, 3 candidates were chosen for further biological investigation: GYKI-39484, GYKI-39521 and GYKI-39541.

Table VI: Antithrombotic activity of 4-substituted phenyl 2,6-anhydro-1,2-dithio-D-manno- and altropyranosides in rat venous thrombosis model (Pescador) 3 h after oral administration (31).



D-manno



D-altro

Structure	R	R_2	ED_{50} (mg/kg)
α-D-manno	OH	CN	2
β-D-manno	OH	CN	2
β-D-manno	OH	C(=NH)OMe	10
β-D-manno	OH	$CSNH_2$	9
β-D-manno	OH	C(=NH)SMe	5
β-D-manno	OH	$C(=NH)NH_2$	13
α-D-manno	OH	NO_2	4
β-D-manno	OH	NO_2	15
β-D-manno	OH	NHAc	20
β-D-manno	N_3	CN	4
β-D-manno	N_3	NO_2	14
α-D-altro	OH	CN	12
β-D-altro	OH	CN	10

The antithrombotic activity of these 3 compounds (Table VII) was studied in various thrombosis models in rabbits. In an extracorporeal arteriovenous shunt model (19), the compounds displayed comparable antithrombotic effects, while greater differences were observed in the Wessler model (stasis/human serum) (33) in rabbits. All compounds were more effective antithrombotics in rats as compared to rabbits.

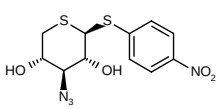
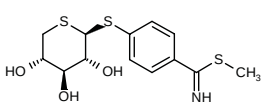
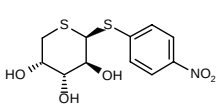
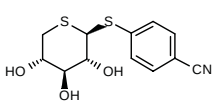
In order to further elucidate the supposed mechanism of action of the compounds, the level of the tissue factor pathway inhibitor (TFPI), a potent inhibitor of the extrinsic coagulation system, was monitored. TFPI is present in the plasma at very low levels but can be released from the endothelial pool into the circulating blood by unfractioned heparin, low molecular weight heparin as well as other glycosaminoglycans (*e.g.*, pentosan polyphosphate) (34). Plasma TFPI concentration was detected by the TFPI activity assay in both rats and rabbits (35, 36). Beciparcil and the new compounds significantly increased TFPI levels in both species (21, 37). This activity was dose- and structure-dependent, persisting for 1-4 h (Table VIII). Accordingly, this effect may contribute to the antithrombotic activity of these compounds.

The anticoagulant effects of the new compounds were evaluated by measuring various clotting parameters (sensitized thrombin time, diluted prothrombin time, Heptest) in rats and rabbits. As expected, all of the compounds exerted only a weak anticoagulant effect. In addition, in a rabbit model of hemorrhage (38, 39), the compounds showed only a marginal effect even with an oral dose of 100 mg/kg (Table IX).

Conclusions

Thioglycosides have been shown to be orally active antithrombotics possessing only weak anticoagulant

Table VII: Antithrombotic activity of selected thioglycosides of 5-thio-pyranosides.

Compound	Structure	ED_{50} (mg/kg) Rat Wessler*	Rat Pescador	Rabbit Wessler*	Rabbit Shunt
GYKI-39484 (RGH-1876)		1.4	0.5	23	22
GYKI-39521 (RGH-1875)		0.6	1.6	60	21
GYKI-39541 (RGH-1962)		1.3	3.6	14	44
Beciparcil		1.1	25	33	41

*Using human serum as activator (33).

Table VIII: Changes in TFPI level after oral doses of thioglycosides (AUC).

Dose (mg/kg)	GYKI-39521	GYKI-39541	GYKI-39484	Beciparcil
		Rabbit		
12.5	189.1	51.4	162.1	35.6
25	232.9	70.8	188.9	49.5
		Rat		
12.5	138.8	61.5	125.6	–
25	185.1	80.0	205.2	71.7

Table IX: Anticoagulant activities and hemorrhage index of thioglycosides (100 mg/kg p.o.).

Parameter (ratio[a])	Species	GYKI-39521 Mean ± SEM	GYKI-39541 Mean ± SEM	Beciparcil Mean ± SEM
dPT	Rat	1.16 ± 0.03**	1.16 ± 0.02**	1.23 ± 0.03
	Rabbit	1.16 ± 0.02*	1.44 ± 0.08**	1.17 ± 0.06
sTT	Rat	7.88 ± 0.18**	1.17 ± 0.04**	6.02 ± 0.78**
	Rabbit	1.19 ± 0.03**	1.29 ± 0.07*	1.35 ± 0.19*
Heptest	Rat	1.58 ± 0.06**	1.22 ± 0.03**	1.35 ± 0.03**
	Rabbit	1.15 ± 0.03*	1.06 ± 0.02	1.27 ± 0.03**
Bleeding time	Rabbit	1.36 ± 0.05*	1.29 ± 0.07*	1.43 ± 0.04*

[a]Value calculated as time ratio between treated and control values. dPT = diluted prothrombin time; sTT = sensitized thrombin time *$p < 0.05$, **$p < 0.01$.

effects. Elevation of the plasma level of tissue factor pathway inhibitor has been suggested to contribute, at least in part, to their antithrombotic effect.

Acknowledgements

This work was supported by the Hungarian Research Council (OMFB) and by the Gedeon Richter Chemical Works Ltd.

References

1. Ofosu, F.A., Gray, E. *Mechanism of action of heparin: Application to the development of derivatives of heparins and heparinoids with antithrombotic properties*. Semin Thromb Haemost 1988, 14: 9-17.

2. Walenga, J.M., Jeske, W.P., Bara, L. et al. *Biochemical and pharmacologic rationale for the development of a synthetic heparin pentasaccharide.* Thromb Res 1997, 86: 1-36.

3. Messmore, H.L. Jr. *Heparin induced thrombocytopenia.* 13th Meet Int Soc Haematol (Sept 3-8, Istanbul) 1995, Lectures 218-20.

4. Teien, A.N., Abildgaard, U., Höök, M. *The anticoagulant effect of heparan sulfate and dermatan sulfate.* Thromb Res 1976, 8: 859-67.

5. Long, W.F. *The anticoagulant activity of dermatan sulfate.* Thromb Res 1988, 18: 493-503.

6. Okayama, M., Kimata, K., Suzuki, S. *The influence of p-nitrophenyl β-D-xyloside on the synthesis of proteochondroitin sulfate by slices of embryonic chick cartilage*. J Biochem 1973, 74: 1069-73.

7. Schwartz, N.B., Galligani, L., Ho, P-L., Dorfman, A. *Stimulation of synthesis of free chondroitin sulfate chains by β-D-xylosides in cultured cells*. Proc Natl Acad Sci USA 1974, 71: 4047-51.

8. Schwartz, N.B. *Regulation of chondroitin sulfate synthesis.* J Biol Chem 1977, 252: 6316-21.

9. Lugemwa, F.N., Esko, J.D. *Estradiol β-D-xyloside, an efficient primer for heparan sulfate biosynthesis*. J Biol Chem 1991, 266: 6674-7.

10. Fritz, T.A., Lugemwa, F.N., Sarkar, A.K. et al. *Biosynthesis of heparan sulfate on β-D-xylosides depends on aglycon structure*. J Biol Chem 1994, 269: 300-7.

11. Fritz, T.A., Agrawal, P.K., Esko, J.D. et al. *Partial purification and substrate specificity of heparan sulfate α-N-acetylglucosaminiltransferase.* Glycobiology 1997, 7: 587-95.

12. Bellamy, F., Horton, D., Millet, J. et al. *Glycosylated derivatives of benzophenone, benzhydrol, and benzhydril as potential venous antithrombotic agents.* J Med Chem 1993, 36: 898-903.

13. Millet, J., Theveniaux, J., Brown, N.L. *The venous antithrombotic effect of LF-1351 in the rat following oral administration.* Thromb Haemost 1992, 67: 176-9.

14. Witczak, Z.J. *Thiosugars: Biological relevance as potential new therapeutics*. Curr Med Chem 1999, 6: 165-78.

15. Bellamy, F., Barberousse, V., Martinet, L. et al. *Thioxyloside derivatives as orally active venous antithrombotics.* Eur J Med Chem 1995, 30 (Suppl.): 101-15.

16. Masson, P.J., Coup, D., Millet, J. et al. *The effect of the β-D-xyloside naroparcil on circulating plasma glycosaminoglycans.* J Biol Chem 1995, 270: 2662-8.

17. Bajusz, S., Szell, E., Bagdy, D. et al. *Highly active and selective anticoagulants: D-Phe-Pro-Arg-H, a free tripeptide aldehyde prone to spontaneous inactivation and its stable N-methyl derivative, D-MePhe-Pro-Arg-H.* J Med Chem 1990, 33: 1729-35.

18. Jackson, C.V., Satterwhite J., Roberts, E. *Preclinical and clinical pharmacology of efegatran (LY-294468): A novel antithrombin for the treatment of acute coronary syndromes.* Clin Appl Thromb Hemost 1996, 2: 258-67.

19. Bagdy, D., Szabó, G., Barabás, É. et al. *Inhibition by D-MePhe-Pro-Arg-H (GYKI-14766) of thrombus growth in experimental models of thrombosis.* Thromb Haemost 1992, 68: 125-9.

20. Bozó, É., Boros, S., Kuszmann, J. et al. *An economic synthesis of 1,2,3,4-tetra-O-acetyl-5-thio-D-xylopyranose and its transformation into 4-substituted-phenyl-1,5-dithio-β-D-xylopyranosides possessing antithrombotic activity.* Carbohydr Res 1998, 308: 297-310.

21. Szabó G., Barabás É., Kuszmann J. et al. *Thioglycosides as orally active antithrombotic agents.* 14th Meet Int Soc Haematol (Stockholm) 1997, Abst P-370.

22. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl 2-deoxy-1,5-dithio-β-D-threo-pentopyranoside*. Carbohydr Res 1997, 299: 59-67.

23. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl and 4-nitrophenyl 1,5-dithio-D-ribopyranosides as well as their 2-deoxy and 2,3-dideoxy derivatives possessing antithrombotic activity*. Carbohydr Res 1999, 321: 52-66.

24. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl 2-azido-2-deoxy- and 3-azido-3-deoxy-1,5-dithio-β-D-xylopyranosides*. Carbohydr Res 1997, 301: 23-32.

25. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl 4-azido-4-deoxy-1,5-dithio-β-D-xylopyranosides*. Carbohydr Res 1997, 302: 149-62.

26. Overend, W.G., Stacey, M. *The chemistry of the 2-desoxysugars.* Adv Carbohydr Chem 1953, 8: 45-91.

27. Horowitz, J.P., Chua, J., Noel, M. *Nucleosides V. The monomesylates of 1-(2'-deoxy-β-D-xylofuranosyl)thimine.* J Org Chem 1964, 29: 2076-8.

28. Mitsuya, H., Weinhold, K.J., Furman, P.A. et al. *3'-Azido-3'-deoxythimidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro.* Proc Natl Acad Sci USA 1985, 82: 7096-100.

29. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl 1,5-dithio-β-D-glucopyranoside and its 6-deoxy, as well as 6-deoxy-5-ene derivatives as oral antithrombotic agents*. Carbohydr Res 1997, 304: 271-80.

30. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl and 4-nitrophenyl 1,5-dithio-L- and -D-arabinopyranosides possessing antithrombotic activity*. Carbohydr Res 1998, 311: 191-202.

31. Bozó, É., Boros, S., Kuszmann, J. *Synthesis of 4-cyanophenyl and 4-nitrophenyl 2,6-anhydro-1,2-dithio-D-manno- and altropyranosides as well as some of their derivatives possessing antithrombotic activity.* Pol J Chem 1999, in press.

32. Davie, E.W., Fujikawa, K., Kisiel, W. *The coagulation cascade: Initiation, maintenance, and regulation.* Biochemistry 1991, 30: 10363-70.

33. Csomor, K., Kárpáti, E., Komlódi, J. et al. *Oral antithrombotic activity of new thioglycosides in rat models of venous thrombosis.* Haemostasis 1998, 28 (Suppl. 2): 463.

34. Sandset, P.M. *The role of tissue factor pathway inhibitor as a physiological anticoagulant.* 13th Meet Int Soc Haematol (Sept 3-8, Istanbul) 1995, Lectures 183-9.

35. Cella, G., Vertolli, U., Naso, A. et al. *Tissue factor pathway inhibitor activity in uremic patients during hemodialysis*. Thromb Res 1996, 6: 671-7.

36. Sandset, P.M., Abildgaard, U., Larsen, M.L. *Heparin induces release of extrinsic coagulation pathway inhibitor.* Thromb Res 1988, 50: 803-13.

37. Szabó, G., Barabás, É., Kedves, R. et al. *Some new thioglycosides as orally active antithrombotic agents.* Haemostasis 1998, 28 (Suppl. 2): 434.

38. Markwardt, F., Klöcking, H.P., Nowak, G. *Antithrombin und antiplasminwirkung von 4-Amidinophenylbrenztraubensaure (APPA) in vivo.* Thromb Haemorrh 1970, 24: 240-7.

39. Bagdy, D., Barabás, É., Szabó, G., Bajusz, S., Szél, E. *In vivo anticoagulant and antiplatelet effect of D-Phe-Pro-Arg-H and D-MePhe-Pro-Arg-H.* Thromb Haemost 1992, 67: 357-65.