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QSAR Study of Some Natural and Synthetic Platelet Aggregation Inhibitors and their Pharmacological Profile

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ABSTRACT

Several well-known synthetic drugs, such as aspirin, elinogrel, and beraprost, and natural drugs, such as eptifibatide and vorapaxar, as platelet aggregation inhibitors are widely used in clinical medicine today. The purpose of this review is a comparative pharmacological analysis of the biological activity of these drugs with natural sulfur-containing hydrocarbons isolated from bacteria, plants, and mineral oils. According to the quantitative structure–activity relationship estimates, these naturally occurring sulfur-containing hydrocarbons are more likely to exhibit antiplatelet properties than those currently used in clinical medicine.

INTRODUCTION

Diseases of the cardiovascular system remain the leading cause of death in many countries. About 18 million people die every year from cardiovascular system diseases worldwide. According to the Centers for Disease Control and Prevention, life expectancy would be 10 years longer if there were not such a high prevalence of cardiovascular disease (CVD), covering all countries of the world (Alzahrani *et al*., 2019; Mirzadeh *et al*., 2022; Mozaffarian *et al*., 2019; Scherer and Schafer, 2022; Weir *et al*., 2016; Wright *et al*., 2018). CVD leads to long-term disability in the adult population and has enormous economic costs. The World Health Organization forecasts are not optimistic: by 2025, about 23 million people will die from CVD, mainly from heart disease and strokes, which are projected to remain the major leading causes of death (Callow, 2006; Mendis *et al*., 2015; Varadarajan *et al*., 2022; Wright *et al*., 2018).

Platelets play a key role in arterial thrombosis, which is a recent event complicating CVD and both peripheral vascular disease and antiplatelet therapy improves the survival of patients with these disorders (Burnouf and Goubran, 2022; Koupenova *et al*., 2017; Paniccia *et al*., 2015).

An antiplatelet drug (antiaggregant) in general, or antiplatelet agent, reduces the ability of platelets to stick together (also known as platelet aggregation) and inhibits the formation of blood clots in blood vessels. Platelet agglutination inhibitors can be synthetic drugs or may be isolated from natural sources that belong to the pharmaceutical drug class, which reduce platelet aggregation and inhibit the formation of blood clots, thereby preventing interruption of blood supply to the brain and, ultimately, a stroke. Such drugs are effective and widely used in primary and secondary prevention of thrombotic cerebrovascular disease (Carvalhal *et al*., 2019; Hirsch *et al*., 2017; Passacquale *et al*., 2022; Roskoski, 2018; Xiang *et al*., 2019).

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Antiplatelet therapy is one of the methods which helps reduce the ability of platelets to form blood clots during primary hemostasis. Various antiplatelet drugs help to reversibly or irreversibly inhibit platelet activation, which reduces the tendency of platelets to adhere to each other and to damage the human blood vessel endothelium (Bouasquevisque *et al*., 2019; Chen *et al*., 2020; Ferlini *et al*., 2019; Hackam and Spence, 2019; Xu *et al*., 2021).

The purpose of this review is to carry out a comparative analysis of known and potential biological activities of synthetic and natural drugs that are currently used in clinical medicine as antiplatelet agents with natural sulfur-containing hydrocarbons that are isolated from natural sources. For detailed characterization of the analyzed compounds' pharmacological potential, we used the computer program PASS (Dembitsky, 2021, 2022; Filimonov *et al*., 2018; Pounina *et al*., 2021).

PASS predicts several thousand biological activities based on analyzing the known structure–activity relationships with an average accuracy of about 96%. Thus, in addition to the previously detected activities in the experiment, the PASS application allows us to identify the most promising but previously unknown activities for further studies (PASS, 2022).

BRIEF DESCRIPTION OF DRUGS CURRENTLY USED IN MEDICINE

According to *Clarivate Analytics Integrity*, 164 synthetic and natural antiplatelet agents are currently included, 25 of which are presented in this work. These drugs were selected given that they have been regularly used in medical practice for the past 20 years. It is known that many drugs that were used before 2000 are not currently used and their use is also prohibited for various reasons. In addition, they must contain sulfur atom(s). All presented antiplatelet agents are divided into two groups. The first group includes only synthetic chemical molecules, while the second group contains metabolites isolated from natural sources. Tables 1–3 present 25 antiplatelet agents that have passed clinical trials and are widely used in medical practice. For each active pharmaceutical ingredient, numerous scientific papers have been published that describe their synthesis and broad aspects of their biological activity.

SYNTHETIC ANTIPLATELET DRUGS

Aspirin

Acetylsalicylic acid (**1**), which is known under the brand name Aspirin, is a medicinal substance that is used in medical practice to reduce pain; treat inflammation, Kawasaki disease (mucocutaneous lymph node syndrome), pericarditis, and rheumatism; and treat or prevent myocardial infarction, strokes, and angina pectoris. The antithrombotic effect of aspirin has long been known and is due to inhibition of platelet function by acetylation of platelet cyclooxygenase on a functionally important amino acid serine. Aspirin is an about 150–200 times more potent inhibitor of the platelet enzyme isoform. In addition, aspirin is the gold standard of antiplatelet agents for the prevention of arterial thrombosis. A complete historical background can be obtained from several review articles and books (Desborough and Keeling, 2017; Miner and Hoffhines, 2007; Schrör, 2016; Vane, 2000; Weissmann, 1991; Wick, 2012). The biological activity demonstrated with aspirin is also widely covered in the scientific literature (Drew and Chan, 2021; Kuzniatsova *et al*., 2012; Montinari *et al*., 2019; Sandler, 1996; Szczeklik *et al*., 2005; Tao *et al*., 2021; Wu, 2003).

Aspirin is a miracle cure that has demonstrated surprising new biological activities for over 150 years. According to the data shown in Table 1, aspirin has antiplatelet, fibrinolytic, antiviral, antithrombotic, antiuremic, rheumatoid arthritis, anti-inflammatory, and anti-infective properties. The PASS predicted these pharmacological effects (Filimonov *et al*., 2018; Pounina *et al*., 2021) and revealed some other biological activities (see Table 1). Aspirin's antiplatelet activity has been known for more than 120 years, and it is now widely used for this purpose worldwide (Dockray, 1905; Williamson, 1902). Table 1 shows what activities aspirin demonstrates (*reported activity*), which were published in the last 40 years (Desborough and Keeling, 2017; Schrör, 2016; Weissmann, 1991), as well as activities (*confirmed activities*) that were confirmed by PASS, as well as additional predicted activities. As we can see from Table 1, 41 activities are characteristic of aspirin, which are obtained when using both one drug or it in conjunction with other drugs.

Figure 1 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities. In addition, Figure 2 shows the predicted and calculated antiplatelet activity of aspirin with high confidence (96%). Figure 3 shows the antipyretic properties of aspirin with over 94% confidence. The structures of synthetic antiplatelet drugs are shown in Figure 4, and the biological activity is shown in Table 2.

Indobufen

Indobufen (**2**, also known as K-3920) was first synthesized more than 40 years ago and was used as a platelet anticoagulant (Fuccella *et al*., 1979; Tamassia *et al*., 1979; Vinazzer, 1979). Since then, it has been widely regarded as an inhibitor of platelet aggregation (Liu *et al*., 2018; Muruganantham *et al*., 2021).

Ticlopidine

Ticlopidine (**3**), known by the tradename Ticlid, was synthesized in 1973, and the platelet aggregation inhibitor was used in humans in the mid-1970s (Thebault *et al*., 1975). It is also currently being used effectively in the antiplatelet therapy associated with coronary disease and type 2 diabetes (Bates, 2019; Flores-Runk and Raasch, 1993; Mori and Geirsson, 2019; Natsuaki and Kimura 2021; Ziada and Moliterno, 2019).

Clopidogrel

Clopidogrel (**4**), an analog of ticlopidine (**3**) and known by the tradename Plavix, was patented in 1982 and approved for medical use in 1998 (Diener, 1998; Féliste *et al*., 1987; Gachet *et al*., 1990). It is an antiplatelet drug used to reduce the risk of CVD and strokes in high-risk individuals. In addition, it is used together with aspirin for myocardial infarctions and after the installation of a stent of the coronary artery (Akkaif *et al*., 2021a; Hankey, 1997; Schrör, 1993; Yao *et al*., 1993). It is included in the World Health Organization's List of Essential Medicines as the safest and most effective drug and is widely used in the United States (Badjatiya and Rao, 2019; Florescu *et al*., 2019; Zeb *et al*., 2018).

Table 1. Reported and confirmed activities of aspirin currently used in medicine.

No	Confirmed activities (Pa)[a]	Reported activity
1	Fibrinolytic (0.960) Antipyretic (0.948) Antiseptic (0.923) Lipid metabolism regulator (0.865) Phobic disorders treatment (0.807) Respiratory analeptic (0.806) Anti-infective (0.787) Anti-inflammatory (0.782) Cytoprotectant (0.742) Platelet adhesion inhibitor (0.739) Neuroprotector (0.712) Antiviral (arbovirus) (0.688) Kidney function stimulant (0.687) Antiuremic (0.671) Erythropoiesis stimulant (0.654) Acute neurologic disorders treatment (0.650) Expectorant (0.649) Mucositis treatment (0.647) Antinephrotoxic (0.646) Antiviral (picornavirus) (0.644) Rheumatoid arthritis treatment (0.637) Anti-ischemic, cerebral (0.633) Keratolytic (0.631) Antihypoxic (0.624) Autoimmune disorders treatment (0.621) Antithrombotic (0.604) Antihypercholesterolemic (0.590) Sickle-cell anemia treatment (0.580) Alopecia treatment (0.579) Vasodilator, peripheral (0.578) Antineurogenic pain (0.570) Antiamyloidogenic (0.568) Antiulcerative (0.567) Analgesic (0.564)	Acute neurologic disorders Alopecia treatment Analgesic Analgesic nephropathy Antiamyloidogenic Anticancer Anti-inflammatory Anti-infective Antihypercholesterolemic Antihypoxic Anti-ischemic, cerebral Antinephrotoxic Antineurogenic pain Antiplatelet Antiproliferative Antiseptic Antithrombotic Antiuremic Antiviral Antiviral (influenza) Antiviral (picornavirus) Antiviral (rhinovirus) Antiulcerative Autoimmune disorders treatment Cyclooxygenase inhibitor Cytoprotectant Cytotoxicity Erythropoiesis stimulant, expectorant Fibrinolytic Keratolytic Lipid metabolism regulator Mucositis treatment Neuroprotector Phobic disorders treatment Platelet adhesion inhibitor treatment Respiratory analeptic Rheumatoid arthritis Sickle-cell anemia treatment Uterine activity Vasodilator, peripheral

[a]Only activities with Pa > 0.5 are shown.

Prasugrel

Prasugrel (**5**), known by the brand name Effient, is used to prevent blood clots and is a platelet inhibitor and irreversible antagonist of the ADP P2Y12 receptor (Gurbel and Tantry, 2008; Niitsu *et al*., 2005; Ray *et al*., 2021; Scott *et al*., 2009). This drug was developed by the Japanese company Daiichi Sankyo Co. and was approved for use in Europe and the United States in 2009 (Dobesh *et al*., 2016; Laine *et al*., 2016; Siller-Matula *et al*., 2017; Siu *et al*., 2016).

Table 2. Pharmacological activities of synthetic antiplatelet drugs currently used in medicine.

No	Antiplatelet and related activities (Pa)[a]	Additional predicted activities (Pa)[a]	Reported activity
2	Fibrinolytic (0.662)	Anti-inflammatory (0.657), Alzheimer's disease treatment (0.548) Neurodegenerative diseases treatment (0.550)	Cyclooxygenase inhibitor
	Platelet adhesion inhibitor (0.524) Antithrombotic (0.511)	Antihypoxic (0.531), anticonvulsant (0.522)	
3	Antithrombotic (0.746)	Acute neurologic disorders treatment (0.786), anticonvulsant (0.678), acetylcholine release	Inhibitor of platelet action
	Platelet aggregation inhibitor (0.507)	stimulant (0.636), antiparkinsonian (0.584), amyotrophic lateral sclerosis treatment (0.577)	
4	Antithrombotic (0.657)	Anti-inflammatory, pancreatic (0.628), acetylcholine release stimulant (0.535)	Inhibitor of platelet activation and aggregation
	Platelet aggregation inhibitor (0.576)	Amyotrophic lateral sclerosis treatment (0.525)	
5	Rheumatoid arthritis treatment (0.659) Cardioprotectant (0.584)	Anticarcinogenic (0.772), antineoplastic (bladder cancer) (0.716)	Cardiac imaging
		Cytostatic (0.690), autoimmune disorders treatment (0.617)	Inhibition of platelet cAMP-phospho-diesterase
	Membrane permeability enhancer (0.544) Antithrombotic (0.501)	Antiviral (arbovirus) (0.615)	
6	Platelet aggregation inhibitor (0.961)	Neuroprotector (0.928), pancreatic disorders treatment (0.773)	Potent inhibitor of platelet aggregation
	Antithrombotic (0.807)	Antiemphysemic (0.596)	
7	Antithrombotic (0.678)	Phospholipase A2 inhibitor (0.777), phospholipase inhibitor (0.758) Acute neurologic disorders treatment (0.705), anticonvulsant (0.507)	Antithrombotic, Anti-ischemic
		Histamine release inhibitor (0.508)	Fibrinolytic
8	Antithrombotic (0.663)	Antineoplastic (lymphocytic leukemia) (0.619), antineoplastic (sarcoma) (0.558)	Inhibitor of the platelet P2Y12 receptor
		Cystic fibrosis treatment (0.555), metabolic disease treatment (0.544)	
			Inhibitor of platelet aggregation
9	Antithrombotic (0.746)	Neuroprotector (0.887), acute neurologic disorders treatment (0.786) Anticonvulsant (0.678), acetylcholine release stimulant (0.636)	Antiplatelet
	Platelet aggregation inhibitor (0.507)	Antiparkinsonian (0.584), psychotropic (0.578)	
10	Fibrinolytic (0.668)	Urologic disorders treatment (0.747), antimetastatic (0.744) Antineoplastic (renal cancer) (0.704)	P2Y12 inhibitor
	Platelet antagonist (0.603) CDK9/cyclin T1 inhibitor (0.542)		Platelet cyclooxygenase inhibitor
11	Antithrombotic (0.685), fibrinolytic (0.623)	Acute neurologic disorders treatment (0.670)	Antithrombotic
		Antineurotic (0.638), anticoagulant (0.520)	Platelet glycoprotein IIb/IIIa inhibitor
	Platelet antagonist (0.583)		
12	Cyclic AMP phosphodiesterase inhibitor (0.803)	Antineoplastic (renal cancer) (0.710), antineoplastic (glioblastoma multiforme) (0.708)	Phosphodiesterase 3A inhibitor
	Leukotriene C4 antagonist (0.599)	Antineoplastic (endocrine cancer) (0.654), fertility enhancer (0.609)	Myocardial ischemia inhibitor
13	Antithrombotic (0.688)	Alzheimer's disease treatment (0.856)	Antiplatelet
	Anticonvulsant (0.599)	Renal failure treatment (0.608), antineoplastic (renal cancer) (0.557)	
14	Thromboxane A2 antagonist (0.868) Thromboxane antagonist (0.859)	Pulmonary hypertension treatment (0.651), antineoplastic (renal cancer) (0.644)	Thromboxane-prostaglandin receptor antagonist Antithrombotic
		Anti-inflammatory, pancreatic (0.624), rhinitis treatment (0.602)	
	Antithrombotic (0.637), antithrombotic (0.591)	Antineoplastic (non-small cell lung cancer) (0.588)	
15	Beta-lactamase AmpC inhibitor (0.680)	Mucolipin-3 activator (0.465)	Antiplatelet
	Beta lactamase inhibitor (0.670)	Nucleotide-binding oligomerization domain-containing protein 2 inhibitor (0.439)	
16	Antithrombotic (0.859)	Neuroprotector (0.854)	Antiplatelet
	Platelet aggregation inhibitor (0.647) Platelet antagonist (0.609)	Muramoyltetrapeptide carboxypeptidase inhibitor (0.834) Vascular (peripheral) disease treatment (0.583)	Pulmonary arterial hypertension inhibitor
17	Platelet aggregation inhibitor (0.703) Galanin receptor antagonist (0.613)	Runt-related transcription factor 1 inhibitor (0.427) Bile salt export pump inhibitor (0.447)	Antiplatelet Treat gout
	Galanin receptor 3 antagonist (0.577)	DNA ligase 1 inhibitor (0.408)	
18	Platelet aggregation inhibitor (0.961) Antithrombotic (0.928)	Pancreatic disorders treatment (0.948) Neuroprotector (0.936)	Strong antiplatelet inhibitor
		Purinergic P2T antagonist (0.706)	
	Platelet antagonist (0.729)		

[a]Only activities with Pa > 0.4 are shown.

Table 3. Pharmacological activities of the natural and seminatural antiplatelet drugs currently used in medicine.

No.	Antiplatelet and related activities (Pa)[a]	Additional predicted activities (Pa)[a]	Reported activity
19	Antithrombotic (0.924)	Antineoplastic (myeloid leukemia) (0.724) Antianginal (0.673)	Antithrombotic
	Anti-ischemic (0.857)	Cell adhesion molecule inhibitor (0.555)	Glycoprotein IIb/IIIa Inhibitor
	Platelet antagonist (0.676)		
	Anticoagulant (0.673)		
20	Thrombin receptor antagonist (0.520)	Neurodegenerative diseases treatment (0.815)	Thrombin inhibitor
		Alzheimer's disease treatment (0.814)	Acute coronary events
21	Purinergic P2Y antagonist (0.996) Antithrombotic (0.815)	Glutamate-5-semialdehyde dehydrogenase inhibitor (0.941) CDP-glycerol glycerophosphotransferase inhibitor (0.934)	Human platelet aggregation inhibitor Anticancer
		Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor (0.929)	
22	Purinergic P2T antagonist (0.670)	Antineoplastic (lymphocytic leukemia) (0.571)	Antithrombotic
	Antithrombotic (0.663)	Cystic fibrosis treatment (0.555), metabolic disease treatment (0.544)	
23	Antithrombotic (0.746)	Neuroprotector (0.887)	Antiplatelet
	Platelet aggregation inhibitor (0.507)	Acute neurologic disorders treatment (0.786), anticonvulsant (0.678) Acetylcholine release stimulant (0.636)	
24	Antithrombotic (0.657)	Neuroprotector (0.775)	Antiplatelet
	Platelet aggregation inhibitor (0.576)	Anti-inflammatory, pancreatic (0.628)	
		Acetylcholine release stimulant (0.535)	
25	Antithrombotic (0.701)	Anticarcinogenic (0.772), antineoplastic (bladder cancer) (0.716)	Antiplatelet
	Platelet aggregation inhibitor (0.598)	Cytostatic (0.690)	

[a]Only activities with Pa > 0.5 are shown.

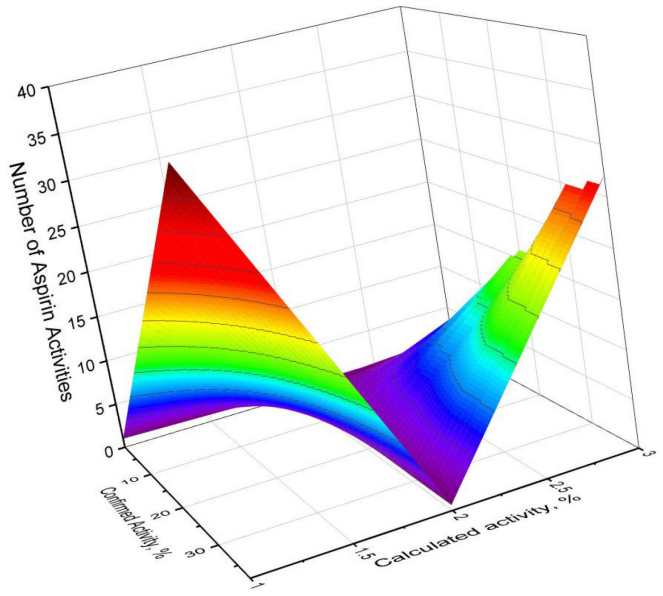

Figure 1. 3D graph of the confirmed and calculated pharmacological activities of acetylsalicylic acid, also known by the trade name *Aspirin*, which is a medication used for inflammation, pain, and other dysfunctions in the human body. Aspirin as a synthetic drug has 41 different activities as shown by various authors over the past 30–40 years. Thirty-eight activities were confirmed using PASS, with the most prominent properties of aspirin being fibrinolytic (96.0%), antipyretic (94.8%), and antiseptic (92.3%) with more than 90% confidence. Other activities are summarized in Table 1.

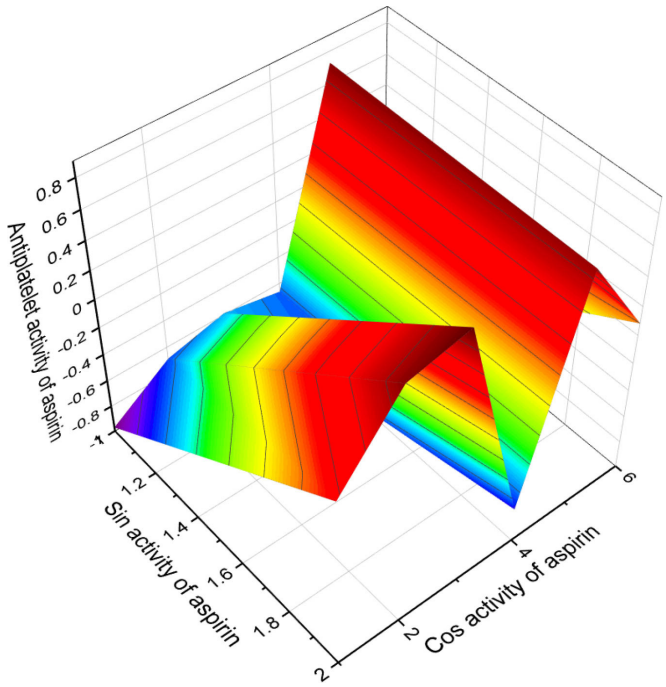

Figure 2. 3D graph shows the predicted and calculated antiplatelet activity of aspirin showing the highest degree of confidence, 96%.

Dipyridamole

Dipyridamole (**6**), patented in 1957 by the name Persantine, inhibits the formation of blood clots, causes the expansion of blood vessels, inhibits the formation of proinflammatory cytokines (MCP-1, MMP-9) *in vitro*, and leads to a decrease in hsCRP in humans. In addition, it is a phosphodiesterase 5A inhibitor, which prevents platelet aggregation by increasing cGMP levels and blocking adenosine reuptake via red blood cells

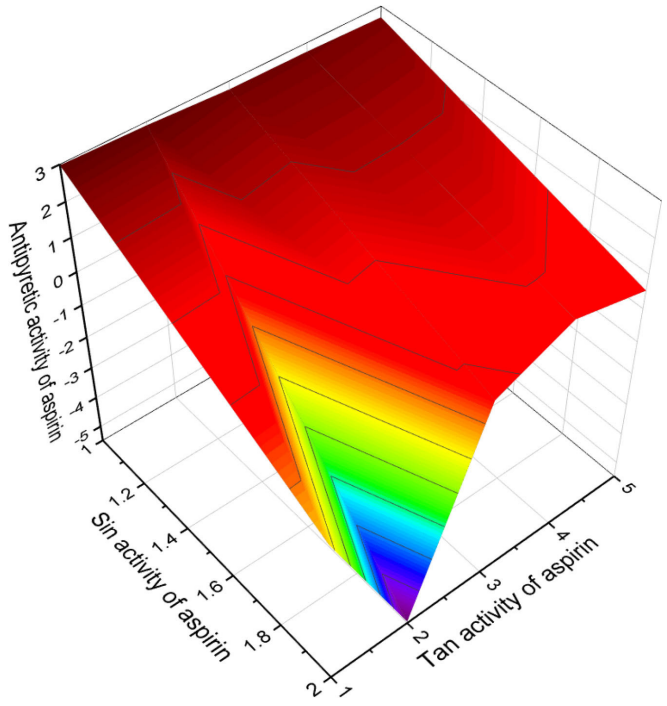

Figure 3. 3D graph shows the predicted and calculated antipyretic activity of aspirin showing the highest degree of confidence, 94.8%.

(Eisert, 2012; FitzGerald, 1987; Jialiken *et al*., 2021; Kapil *et al*., 2017; Zakeri and Nimjee, 2018). Originally, in the late 1950s and early 1960s, Persantine was used to treat coronary heart diseases that eventually lead to myocardial infarction (Degraff and Lyon, 1963; Greif, 1960; Junemann, 1959; Knabe, 1964; Tetzlaff and Tetzlaff, 1959).

Figure 5 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities.

Defibrotide

Defibrotide (**7**) is known by the brand name Defitelio, and its mechanism of action is poorly understood. However, it is used to treat vessel-occlusive liver disease in people who have undergone bone marrow transplantation. In combination with other drugs, it is used as an antiplatelet agent (Berge and Sandercock, 2002; Fareed *et al*., 2013; Onuora, 2022; Palmer *et al*., 2013).

Cangrelor

Cangrelor (**8**), known by the tradename Kengreal (in the USA) or Kengrexal (in Europe), is a P2Y12 FDA inhibitor and has been known as an antiplatelet agent since 2015. It is a high affinity, reversible P2Y12 receptor inhibitor, that causes almost complete inhibition of the ADP-induced platelet aggregate (De Luca *et al*., 2021; Gachet, 2008; Storey and Sinha, 2016; Tello-Montoliu *et al*., 2012; Ueno *et al*., 2010).

Naftazone

Naftazone (**9**, β-naphthoquinone monosemicarbazone) was first synthesized in France in the early 1970s and was used to prevent bleeding in prostate surgery (Charles and Coolsaet, 1972; Delwaide *et al*., 1974). It was later studied as an agent that prevents platelet coagulation and was used in the treatment of Parkinson's disease and against MCF-7 human breast cancer cells (Chen *et al*., 2004; Corvol *et al*., 2019; Kitchens *et al*., 2020; McArdle and Erxleben 2021; McGregor *et al*., 1999).

Ticagrelor

Ticagrelor (**10**) is an inhibitor of platelet aggregation and is a P2Y12 receptor antagonist. It has been used in the European Union since 2010 and in the USA since 2011 (Akkaif *et al*., 2021b; Husted and van Giezen, 2009; Gurbel *et al*., 2010a,b; Marczewski *et al*., 2010; Nicolau *et al*., 2018).

Tirofiban

Tirofiban (**11**, trade name Aggrastat) is a synthetic nonpeptide platelet aggregation inhibitor that belongs to a class of antiplatelet agents called glycoprotein IIb/IIIa inhibitors. The GP IIb/IIIa receptors are fibrinogen attachment sites that promote platelet aggregation. Tirofiban was developed by the Merck chemical group of George Hartman, Melissa Egbertson, and Wasyl Halczenko in the early 1990s. Interestingly, tirofiban is a modified version of the molecule (mimics part of the natural protein) found in the venom of the scaly viper *Echis carinatus*, also known as "carpet" vipers, living in areas with sandy soil and rock outcrops in Africa and some countries of the Middle East (Coller, 2001; Dogne *et al*., 2002; Egbertson *et al*., 1994; Gong *et al*., 2020; Hartman *et al*., 1992; Menozzi *et al*., 2005; Tang *et al*., 2021).

Cilostazol

Cilostazol (**12**), known by the brand name Pletal, is a selective inhibitor of phosphodiesterase type 3 with a therapeutic focus on increasing cAMP. An increase in cAMP leads to an increase in the active form of protein kinase A, which is directly related to the inhibition of platelet aggregation, thereby exerting its vasodilating effect. This drug was approved for medical use in the United States in 1999 but is not yet available in Canada or the United Kingdom (Brown *et al*., 2021; Comerota, 2005; Goto, 2005; Hidaka *et al*., 1991; Hiatt, 2005; Kwon and Kim, 2016; Reilly and Mohler, 2001).

Elinogrel

Elinogrel (**13**) was developed by Portola Pharmaceuticals (an American clinical-stage biotechnology company) as an experimental antiplatelet drug that acts as a P2Y12 inhibitor. In addition, it has been used in antiplatelet therapy for acute coronary syndromes. Since 2012, its production has been discontinued (Bonadei *et al*., 2014; Gurbel *et al*., 2010; Lordan *et al*., 2021; Michelson, 2011; Müller *et al*., 2012).

Terutroban

Terutroban (**14**) is an antiplatelet agent that was developed by *Servier Laboratories* (Suresnes, France). It is a selective antagonist of thromboxane prostanoid and is an orally active drug in clinical development for the secondary prevention of acute thrombotic complications (Baidildinova *et al*., 2021; Coccheri, 2010; Franchini and Mannucci, 2009; Verbeuren, 2006).

Triflusal

Triflusal (**15**, known by the Disgren or Grendis trade name) was synthesized in Uriach laboratories in the late 1970s

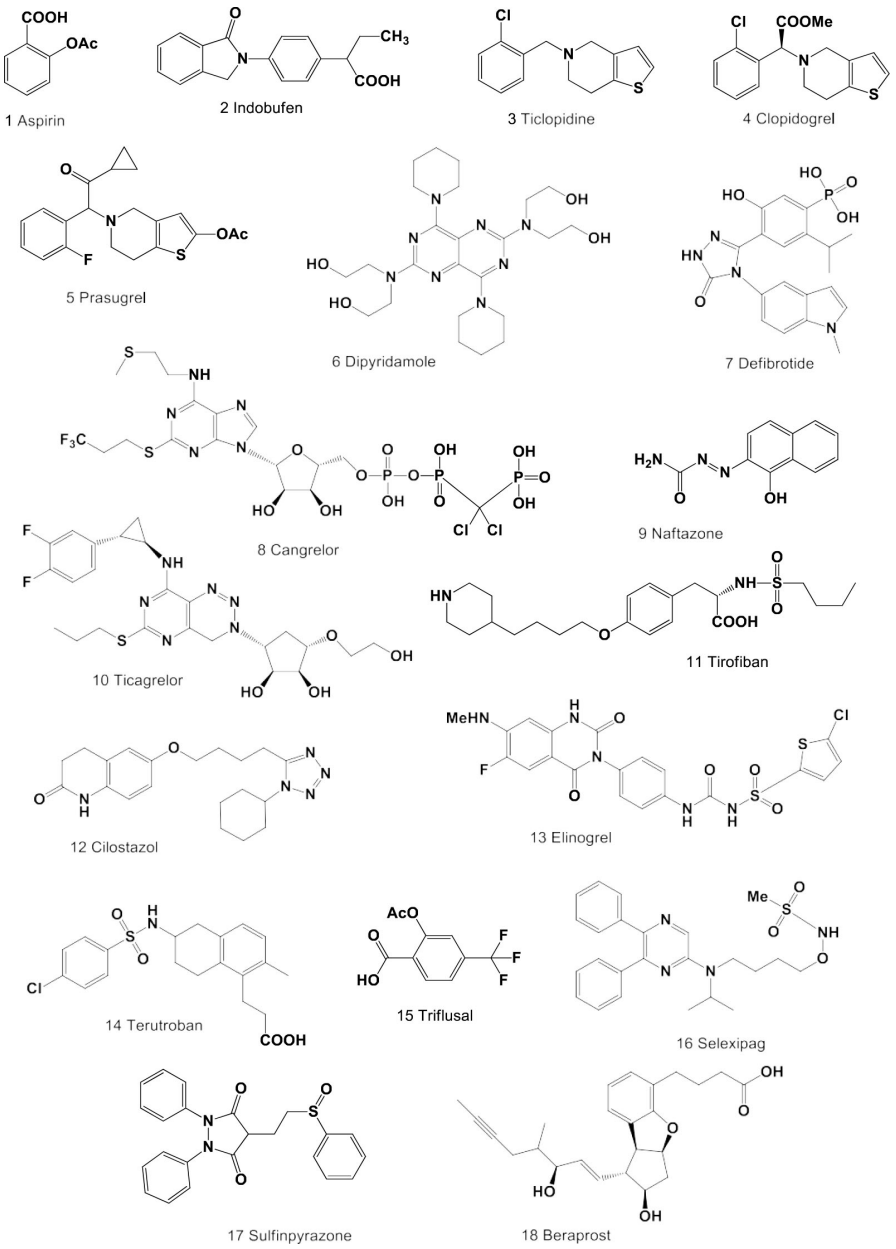

Figure 4. Synthetic antiplatelet drugs currently used in medicine. The pharmacological profiles and biological activities are shown in Table 2.

and has been commercially available in Spain and France since 1981 (Garcia-Rafanell and Morell, 1977; Garcia-Rafanell *et al*., 1979). Its salicylate is structurally like acetylsalicylic acid but is not a derivative of this acid (McNeely and Goa, 1998). It is an inhibitor of platelet aggregation and is available in more than 25 countries in Europe, Asia, Africa, and America. In combination with aspirin and other drugs, it has a good effect in inhibiting platelet aggregation (Huang *et al*., 2017; Kalantzi *et al*., 2019; Milionis *et al*., 2016; Yun *et al*., 2014) and has a neuroprotective effect (Kim *et al*., 2017).

Selexipag

Selexipag (**16**) was synthesized by *Actelion Pharmaceuticals* Ltd. and Nippon Shinyaku in the mid-2000s as a medicine for the treatment of pulmonary arterial hypertension (Kuwano *et al*., 2007; Nakamura *et al*., 2007). It is a highly selective nonprostanoid agonist of long-acting prostacyclin receptors and is used in antiplatelet therapy (Barnes *et al*., 2019; Coghlan *et al*., 2019; Genecand *et al*., 2021; Scott, 2016; Sitbon and Morrell, 2012; Skoro-Sajer and Lang, 2014).

Sulfinpyrazone

Initially, sulfinpyrazone (**17**, also known as anturan) was developed by Ciba-Geigy AG (Swiss Pharm Co. Ltd.) in the mid-1950s to treat gout, as well as an analog of phenylbutazone, but this drug does not have the properties of phenylbutazone (Brodie *et al*., 1954; Montgomery and Ogryzlo, 1960; Persellin, 1961; Wilhelmi and Currie, 1954). It shows a uricosuric and pronounced antiplatelet effect. It is suggested that the effect of sulfinpyrazone on platelet function may be associated with inhibition of

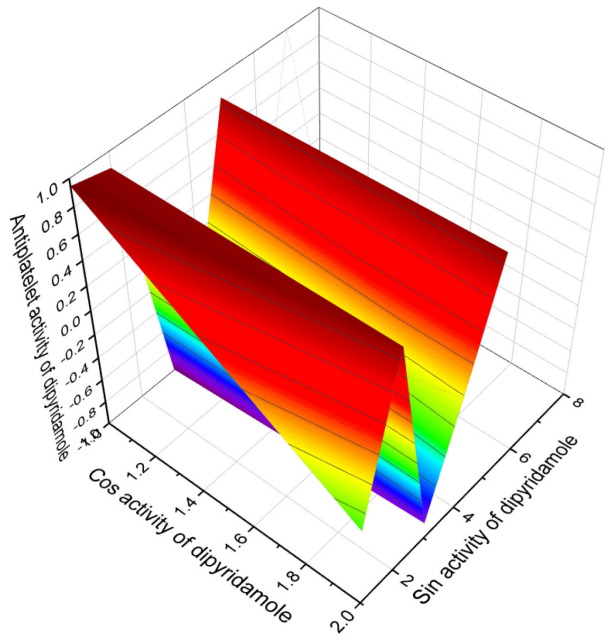

Figure 5. 3D graph shows the predicted and calculated antiplatelet activity of the synthetic antiplatelet agent dipyridamole (**6**) showing the highest degree of confidence, 96%.

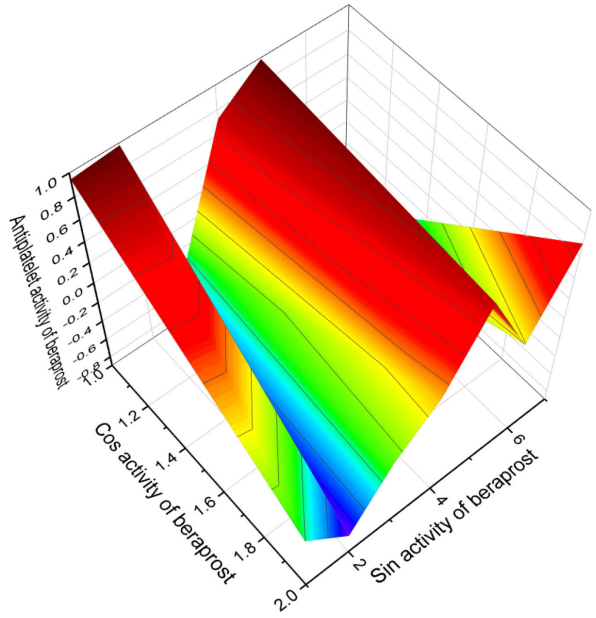

Figure 6. 3D graph shows the predicted and calculated antiplatelet activity of the synthetic antiplatelet agent beraprost (**18**) showing the highest degree of confidence, 96%.

prostaglandin synthesis. Sulfinpyrazone does not replace the well-known and traditional anticoagulant agents in the treatment of venous thrombosis, but it is an important drug for the treatment of conditions associated with arterial thrombosis and, possibly, for the prevention of recurrent venous thrombosis (Gallus, 1985; Jafri, 1991; Keyser, 1993; Margulies *et al*., 1980; Orhan and Deniz 2021).

Beraprost

Beraprost (**18**) contains a unique tricyclic core, which has four adjacent stereocenters, is an analog of prostacyclin PGI2, which demonstrated a strong antiplatelet effect measured by the Born (1962) method in the 1960s, and acts as an effective vasodilator. The effect was tested in platelet-rich plasma obtained from humans and some experimental animals, including rabbits, rats, guinea pigs, dogs, and cats. In addition, PGI2 has attracted much attention due to its ability to stimulate axonal remodeling of damaged neural networks after central nervous system disease (Callow, 2006; Wright and Wall, 2018). As a vasodilator and antiplatelet agent, it is widely used in some Asian countries in Japan, South Korea, and China (Nakura *et al*., 2020; Shen *et al*., 2019; Sharmin *et al*., 2021). Figure 6 shows the 3D graph of a wide range of confirmed and the calculated pharmacological activities.

NATURAL OR SEMINATURAL ANTIPLATELET DRUGS

Eptifibatide

Eptifibatide (**19**) is a cyclic heptapeptide derived from the disinterring protein (P22827) found in the venom of a southeast rattlesnake (*Sistrurus miliarius barbouri*) (Millennium Pharmaceuticals/Schering-Plow/Essex). It belongs to the class of arginine–glycine–aspartate mimetics and reversibly binds to platelets, has a short half-life, and is widely recognized. In addition, it is used to reduce the risk of acute ischemic events in the heart. The drug is usually used with aspirin or heparin (Dogne *et al*., 2002; Goa and Noble, 1999; Nana *et al*., 2021; O'Shea *et al*., 2002; Phillips and Scarborough, 1997; Tempelhof *et al*., 2012). The structures of natural or seminatural antiplatelet drugs are shown in Figure 7, and the biological activities are shown in Table 3. Figure 8 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities

Vorapaxar

Vorapaxar (**20**), known as SCH 530348, is a thrombin receptor antagonist, namely the protease-activated receptor, PAR-1, which has been synthesized from the natural himbacine product (Clasby *et al*., 2007; Chelliah *et al*., 2014). It is known that himbacine was isolated from the bark of rain forest trees *Galbulimima belgraveana* and *G. baccata* native to Papua New Guinea, Indonesia, and Northern Australia (Lan *et al*., 2018). This drug is part of the PAR-1 antagonist family, which inhibits platelet aggregation associated with thrombin. A study of the mechanism of action of vorapaxar showed that it works in a different way than other antiplatelet drugs, such as aspirin and P2Y12 inhibitors (Bhat *et al*., 1977; Gurbel *et al*., 2011; Poole and Elkinson, 2014; Tantry *et al*., 2015; Ten Cate *et al*., 2021; Wang, 2015; Ungar *et al*., 2016). Figure 9 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities.

Forskolin

Forskolin (**21**, also called coleonol) is a labdanic diterpenoid found in extracts from the roots of an Indian tropical plant (*Coleus forskohlii*) (Mohamed Saleem, 2013; Sapio *et al*., 2017). For centuries, it was used in traditional Indian and Chinese herbal medicine to treat various diseases such as asthma and urinary tract infections and has recently found application in the fight against cancerous tumors (Adnot *et al*., 1982; Bednarek *et al*., 2020). Forskolin has been shown to be a potent inhibitor of

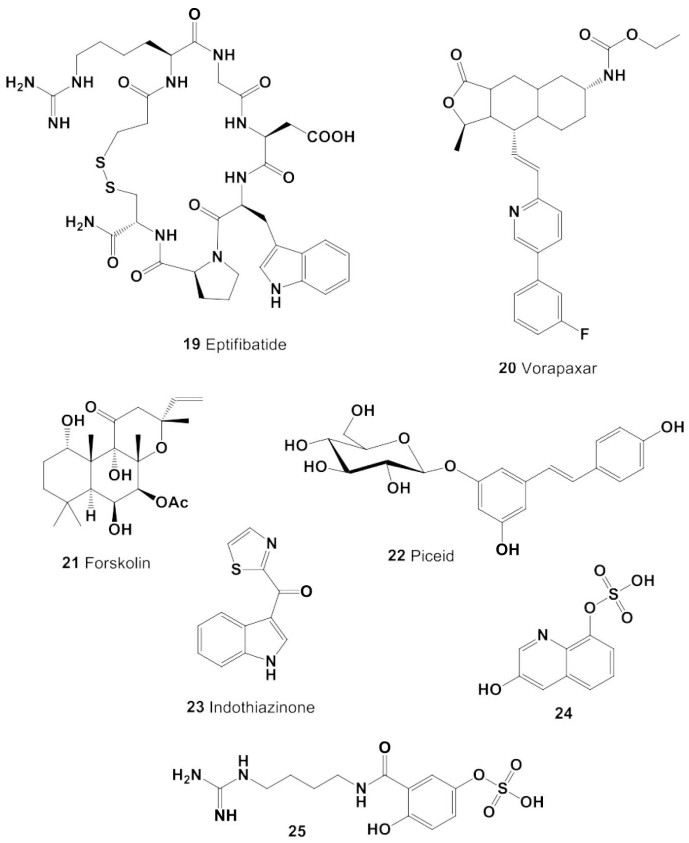

Figure 7. Natural and seminatural antiplatelet drugs currently used in medicine. The pharmacological profiles and biological activities are shown in Table 3.

human platelet aggregation and is used in antiplatelet therapy (De Souza *et al*., 1983; Ju *et al*., 2021; Romero-Pérez *et al*., 1999).

Piceid. Piceid (**22**) is a resveratrol glycoside that is present in the juice of red and white grapes (Lamuela-Raventos *et al*., 1995; Pezet *et al*., 2004). Many authors believe that, due to the content of resveratrol glycoside and other phenolic products, grape juice can have a beneficial effect on the health of those who cannot drink wine (Bonechi *et al*., 2017). Resveratrol is known to affect the inhibition of platelet adhesion and aggregation, as well as conformational changes in fibrinogen caused by adrenaline (Olas and Wachowicz, 2005). In addition, resveratrol reduces lipid peroxidation, oxidation, and nitration of platelet and plasma proteins and affects the function of blood platelets, which play an important role not only in the hemostatic process but also in the pathogenesis of CVD (Herrmann *et al*., 2017).

Indothiazinone

Indothiazinone (**23**) is an indolyl thiazolyl ketone that was discovered in cultures of novel myxobacteria strain 706 (family Sorangiineae) and was derived from compost (Jansen *et al*., 2014; Yang *et al*., 2017). Based on experimental data, indothiazinone was identified as a potential antiplatelet agent. It limits the thrombin and adenosine diphosphate-dependent distribution of human platelets on the fibrinogen matrix and can be used to develop antiplatelet agents with a new mode of action (Lee *et al*., 2016).

3-Hydroxyquinolin-8-yl hydrogen sulfate (24) and 3-[(4-carbamimidamido-butyl)-carbamoyl]-4-hydroxyphenyl hydrogen sulfate (25)

These low-molecular-weight anticoagulants, sulfated quinoline alkaloid (**24**) and acylated polyamine (**25**), were found in the extracts of Chinese red scolopendrium (*Scolopendra subspinipes mutilans*). These components were isolated, and their structures were established using chemical and physical methods (Block *et al*., 1984). Studies have shown that both bleached low-molecular-weight alkaloids (**24** and **25**) demonstrate antithrombotic and antiplatelet activities.

NATURAL SULFUR-CONTAINING HYDROCARBONS AS POTENTIAL ANTIPLATELET DRUGS

Ajoene (**26A**) and deoxygenated ajoene (**26**) were isolated from garlic, and their structures were determined and synthesized in 1984 in the Block laboratory (Fenwick *et al*., 1985a). The structures of ajoene (**26A**) and the ajoene analog (**26**) are shown in Figure 10, and the biological activities are shown in Table 3. An ajoene is known to be an organosulfur compound contained in the extracts of garlic (*Allium sativum*). Interestingly, the name comes from *ajo*, the Spanish word for garlic (Fenwick *et al*., 1985b, 1985c; Yoshida *et al*., 1979). The antifungal activity of garlic was first studied more than 40 years ago, and in experiments ajoene showed the strongest activity against *Aspergillus niger* and *Candida albicans* at <20 μg/ml (Apitz-Castro *et al*., 1986a).

As far back as 1986, ajoene (**26A**) and/or the ajoene analog (**26**) were shown to demonstrate platelet aggregation inhibition, which was later proven by many investigators (Apitz-Castro *et al*., 1986b; 1992; Agarwal, 1996; Jamaluddin *et al*., 1988). MacDonald and Langler (2000) found that some simple organosulfur compounds isolated from garlic showed antithrombotic activity, and this activity is associated with disulfides (Ledezma *et al*., 2009). A wide range of activities including anticancer, hepatoprotective, gastroprotective, antidiabetic, antiobesity, neuroprotective, and renoprotective properties have also been shown for ajoene and other sulfur-containing metabolites (Clapperton *et al*., 1989; Patiño-Morales *et al*., 2021; Shang *et al*., 2019). The structures of natural sulfur-containing antiplatelet drugs are shown in Figure 10, and the biologic activities are shown in Table 4. Figure 11 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities of (**26A**).

It is known that mammals belonging to the Mustela family emit foul-smelling secretions when in danger (Brinck *et al*., 1983; Crump, 1978). An analysis of these odors was studied, and di-2-butenyl disulfide (**27**) was detected in the volatiles of *Mustela altaica* (Andersen and Bernstein, 1980; Hamilton *et al*., 1999). Therefore, the odors of low-molecular-weight compounds of divalent sulfur are usually very intense and irritate people, as well as other animals; in addition, many of these second secondary metabolites are found in plants and are also represented in mammalian secretions (Wei *et al*., 2007). Figure 12 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities.

It is known that thiadiamondoids were first found in crude oil in small quantities, but their quantitative content increases with the thermochemical reduction of sulfates using sodium sulfate as an oxidizing agent in the presence of elemental sulfur and deionized

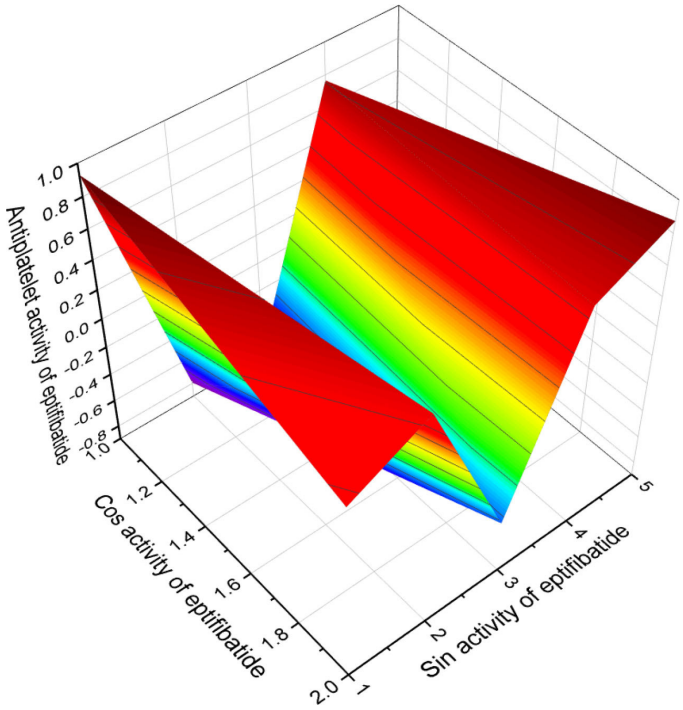

Figure 8. 3D graph shows the predicted and calculated antiplatelet activity of the natural antiplatelet agent called eptifibatide (**19**), a cyclic heptapeptide from the disinterring protein (P22827), which was detected and isolated from the venom of a southeast rattlesnake (*Sistrurus miliarius barbouri*) with the highest degree of confidence, 92%.

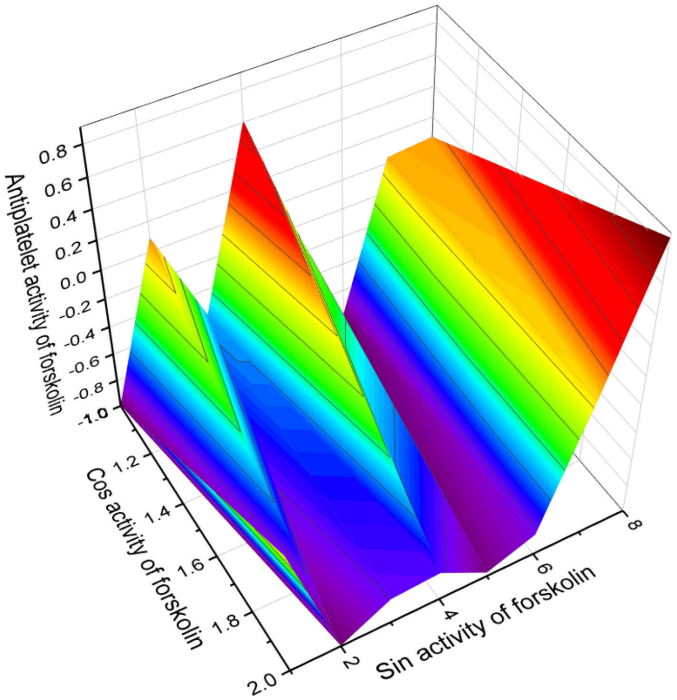

Figure 9. 3D graph shows the predicted and calculated antiplatelet activity of the natural antiplatelet agent forskolin (**21**, also called coleonol), a labdanic diterpenoid isolated in the extracts from the roots of an Indian tropical plant (*C. forskohlii*), with the highest degree of confidence, 92.4%.

water. This procedure suggests that thiamondoids or diamondolioliols are formed during the thermochemical treatment of crude oil, and sulfur-containing compounds [4,8,10-trithia-adamantane (**28**) and 5,10,13-trithia-diadamantane (**32**)] were isolated from such oil (Abu-Awwad, 2010; Dahl *et al*., 1999; Wei *et al*., 2011). Figure 13 shows the 3D graph of a wide range of confirmed and calculated pharmacological activities of compound 28.

Four di- (**29** and **30**), tetra- (**30**, **34**), and pentasulfide (**36**) derivatives were isolated from freshly cut garlic (*A. sativum*), onion (*Allium cepa*), and leek (*Allium porrum*), which exhibit antimicrobial and antibacterial activity (Abu-Lafi *et al*., 2004; Block, 1985; Block *et al*., 1996; Dembitsky *et al*., 2007a, 2007b; Kallio and Salorinne, 1990; Sommano *et al*., 2016; Vizer *et al*., 2015; Wijers *et al*., 1969). 1-Isopentyl-2-(prop-1-en-1-yl) disulfide (**31**) and compound (**33**) were found in three varieties of garlic (*A. sativum*) commonly used to produce essential oils in the northern Thai market, such as "Thai," "Ping-Pong," and "Chinese," and in various sulfur-containing flavor volatiles in foods (Peppard, 1981; Shankaranarayana *et al*., 1974).

Sesquiterpene episulphide, 6,7-epithiogermacrene D (**34**) was isolated from hops and has shown anti-inflammatory and antineoplastic activity and demonstrated platelet aggregation properties (Hough *et al*., 1982; Lermusieau and Collin, 2003; Peppard *et al*., 1980; Poroikov *et al*. 2017; Xiong *et al*., 2018).

Diallyl disulfide (**35**, 4,5-dithia-1,7-octadiene) is a well-known metabolite that has a strong garlic smell and is produced by the decomposition of allicin, which is released by grinding garlic from garlic and some other plants of the *Allium* genus (Kallio and Salorinne, 1990). Diallyl disulfide has been shown to inhibit the growth and development of breast cancer, adenocarcinoma cells, and invasive ductal carcinoma (Bauer *et al*., 2014; Jo *et al*., 2008; Wratten *et al*., 1976; Yin *et al*., 2018).

It is known that cyclic natural polysulfides such as di-, tri-, and tetrathiacycloalkanes are found in marine green (chlorophytes), brown (phaeophytes), and red (rhodophytes) algae and some invertebrates (Dembitsky and Srebnik, 2002; Jiang *et al*., 2012; Gmelin *et al*., 1981; Rezanka and Dembitsky, 2002), plants (Da Silva *et al*., 2014; Huang *et al*., 2009; Lane *et al*., 2004; Sobik *et al*., 2007), and are also synthesized by some bacteria (Goeke, 2002; Ritzau *et al*., 1993; Schulz *et al*., 2010). Bioactive cyclic natural polysulfides (37, 38, 39, and 46; the structures are shown in Figure 14, and the biological activities are shown in Table 4) were identified from the extracts of two bacterial *Cytophaga* strains (CFB phylum) isolated from biofilms from the North Sea (Ritzau *et al*., 1993).

Volatile sulfur-containing hydrocarbons (**41**) and (**45**) were detected by GC-MS in grapefruit and orange juice (Cannon and Ho, 2018), and compound (**47**) was found among sulfur-containing metabolites in tropical fruits (Yoshida *et al*., 1987). Unusual sulfur-containing hydrocarbons α-mintlactone (**43**) and isomintlactone (**44**) and (**50**) were identified as minor and trace volatile components of peppermint oil Mitcham (*Mentha piperita*) (Takahashi *et al*., 1981; Tava *et al*., 2007). Mintsulfide has also been found in trace amounts in essential oils in various plant species such as *Artemisia pallens*, *Bituminaria bituminosa*, *Cananga odorata*, *Cymbopogon winterianus*, *Hyssopus officinalis*, *Ocimum bacilicum*, *Matricaria chamomilla*, *Mentha spicata*, *Mentha piperita*, *Mentha arvensis*, *Stachys sylvatica*, *Solidago altissima*, *Rosa damascena*, *Piper nigrum*, and *Pelargonium graveolens* (Murakami *et al*., 2006; Tava *et al*., 2007; Tirillini *et al*., 2004).

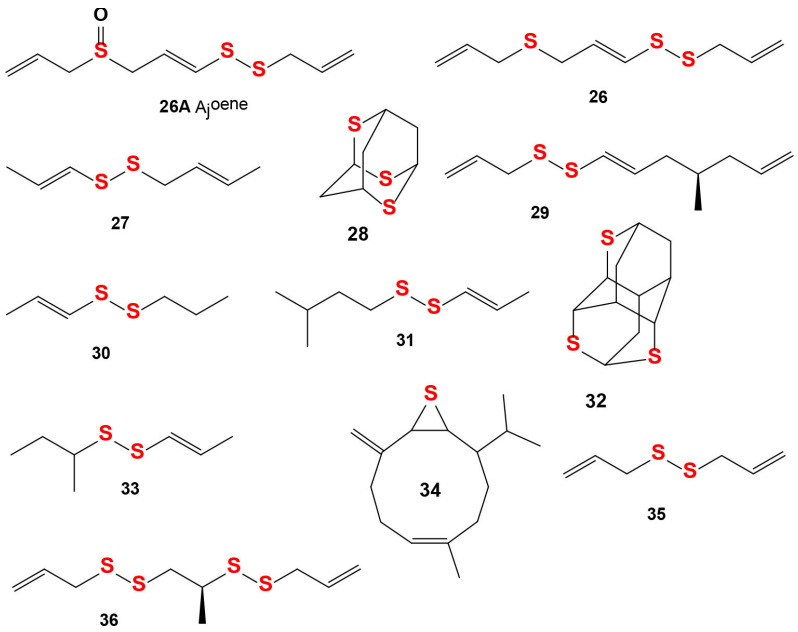

Figure 10. Natural sulfur-containing compounds as potential antiplatelet agents. The pharmacological profiles and biological activities are shown in Table 4.

The *Humulus lupulus* plant is a species of flowering plant belonging to the family of hemp (Cannabaceae) and native to Europe, Asia, and North America. It is widely known throughout the world as a raw material for the brewing industry (Zanoli and Zavatti, 2008). Hop cones contain polyphenolic compounds and are widely used for canning beer and give it a characteristic aroma and taste. In addition, hop cones have long been used for medicinal purposes, especially for the treatment of sleep disorders, as a mild sedative (Orr and Sinninghe Damsté, 1990). Two bioactive compounds (**48**) and (**49**) were identified in hop (*Humulus lupulus*) which is cultivated all over the world for the brewery industry (Cannon and Ho, 2018).

Sulfur-containing compound (**47**) and triterpenoid (**51**) were found in fossil sour oil using high-resolution GC-MS (Orr and Sinninghe Damsté, 1990).

COMPARISON OF BIOLOGICAL ACTIVITIES OF NATURAL AND SYNTHETIC COMPOUNDS

Nowadays, it is generally accepted that drug-like compounds' biological activities depend on their structural formula (Filimonov and Poroikov, 2008). Despite the activity cliffs (Stumpfe *et al*., 2019), which may be considered as violating this statement, structure–activity relationships (SAR) are widely used in medicinal chemistry for finding and optimization of novel pharmaceutical agents (Poroikov, 2020, Poroikov, 2020; Ermolenko *et al*., 2020; David 2002, Vil *et al*., 2019a,b,c,d).

Computer program PASS (Dembitsky *et al*., 2021; Filimonov *et al*., 2018; Pounina *et al*., 2021), whose development started over 30 years ago, currently predicts more than 5,000 pharmacological effects, molecular mechanisms of action, pharmacological effects, toxicity, and side effects, antitargets, transporters-related interactions, genes expression regulation, and metabolic terms (Druzhilovskiy *et al*., 2017). The average accuracy of PASS predictions achieved 96% due to the utilization of chemical descriptors and a robust mathematical approach for SAR analysis (Al Quntar *et al*., 2020; Dembitsky *et al*., 2021; Poroikov, 2020).

Freely available in the Internet web resource, PASS Online (PASS Online URL www.way2drug.com/passonline) is used by more than 20,000 users from 100 countries. Based on PASS predictions, the researchers identify the most promising assays for the synthesized compounds and select the virtually designed molecules with the required activities for synthesis (Al Quntar *et al*., 2020; Savidov *et al*., 2018).

In this study, we used PASS to estimate the analyzed natural and synthetic platelet aggregation inhibitors' general pharmacological potential. Probabilities of belonging to the class of "actives" Pa were estimated for more than 4,200 pharmacological effects and molecular mechanisms of action. Pa values vary from zero to one; the higher the Pa value is, the higher the probability of confirming the predicted activity in the experiment is. On the other hand, estimated Pa values might be relatively small for some activities if the analyzed compound is less like the "actives" from the PASS training set. Thus, PASS prediction interpretation requires considering two contradictory issues: "high probability of activity" versus "high structural novelty." The researcher decides which issue is more critical, depending on the task or the project (Dembitsky *et al*., 2020a, 2020b, 2020c; 2021a, 2021b; Poroikov, 2020).

Currently, tens of thousands of articles have been published that suggest synthesized or natural compounds as a preventative measure or treatment for dementia, but it turns out that more than 99% of the proposed compounds are not suitable for these purposes. The idea of using the PASS algorithm to test all drugs that are currently used in clinical medicine as antiplatelet agents was born long ago, but some time ago this idea was successfully implemented. By analyzing the data obtained using PASS for synthetic (**1**–**18**) and natural (**19**–**25**) antiplatelet drugs currently used in medicine, as well as natural sulfur-containing hydrocarbons (**26**–**51**), we can assume that sulfur-containing

Table 4. Pharmacological activities of natural SC hydrocarbons as potential antiplatelet drugs with high reliability from 78% to 99%.

No.	Antiplatelet and related activities (Pa)[a]	Additional predicted activities (Pa)[a]	Reported activity
26A	Platelet antagonist **(0.997)**	Apoptosis agonist (0.998), antineoplastic (myeloid leukemia) (0.996)	Antiplatelet
	Antithrombotic (0.779)	Lipoprotein disorders treatment (0.995)	Antifungal
		Antineoplastic (0.990), chemoprotective (0.859)	Antimicrobial
		Antiviral (HIV) (0.830), antioxidant (0.816)	Antitumor
		Inflammatory bowel disease treatment (0.704)	Antiproliferative
		Antifungal (0.689), atherosclerosis treatment (0.569)	Antimycobacterial
26	Platelet antagonist **(0.996)**	Antineoplastic (myeloid leukemia) (0.995), neuroprotectant (0.897)	Antithrombotic, antifungal
	Antithrombotic (0.604)	Chemoprotective (0.892), hypolipemic (0.838), antiviral (HIV) (0.764) Prostate cancer treatment (0.516)	Antidiabetic, antiobesity, Neuroprotective, renal protective
27	Platelet antagonist **(0.993)**	Apoptosis agonist (0.997), antineoplastic (myeloid leukemia) (0.991)	No information
	Platelet aggregation inhibitor **(0.942)**	Antiviral (HIV) (0.686), atherosclerosis treatment (0.661)	
28	Platelet aggregation inhibitor (**0.988**)	Antiasthmatic (0.993), antiallergic (0.992), antiviral (arbovirus) (0.593)	No information
		Alopecia treatment (0.553), leukopoiesis stimulant (0.549)	
29	Platelet antagonist **(0.971)**	Apoptosis agonist (0.996), antineoplastic (myeloid leukemia) (0.983)	No information
	Antithrombotic (0.593)	Atherosclerosis treatment (0.724), antiviral (0.577)	
30	Platelet antagonist **(0.967)**	Antineoplastic (myeloid leukemia) (0.985), apoptosis agonist (0.985)	No information
		Antiviral (Arbovirus) (0.625), chemoprotective (0.593)	
31	Platelet antagonist **(0.916)**	Antineoplastic (myeloid leukemia) (0.981), apoptosis agonist (0.975) Lipoprotein disorders treatment (0.807), chemoprotective (0.563) Leukopoiesis stimulant (0.525)	No information
32	Platelet aggregation inhibitor **(0.909)**	Antiasthmatic (0.968), antiallergic (0.953), antiarrhythmic (0.944)	No information
		Cardiotonic (0.932), atherosclerosis treatment (0.784)	
33	Platelet antagonist (0.875)	Antineoplastic (pancreatic cancer) (0.983), antineoplastic (myeloid leukemia) (0.982), antimitotic (0.733)	No information
	Platelet aggregation inhibitor (0.786)		
34	Platelet aggregation inhibitor (0.866)	Renin release stimulant (0.780), anti-inflammatory (0.770)	No information
		Antineoplastic (0.772), apoptosis agonist (0.684)	
35	Platelet antagonist (0.785)	Apoptosis agonist (0.995), antineoplastic (myeloid leukemia) (0.961)	Antithrombotic
		Atherosclerosis treatment (0.921), leukopoiesis stimulant (0.694)	Antitumor
36	Platelet antagonist (0.785)	Insulin sensitizer (0.988), atherosclerosis treatment (0.988), prostate cancer	No information
	Antithrombotic (0.674)	treatment (0.934), antineoplastic (myeloid leukemia) (0.923)	

[a]Only activities with Pa > 0.5 are shown. Abbreviations: SC: sulfur-containing.

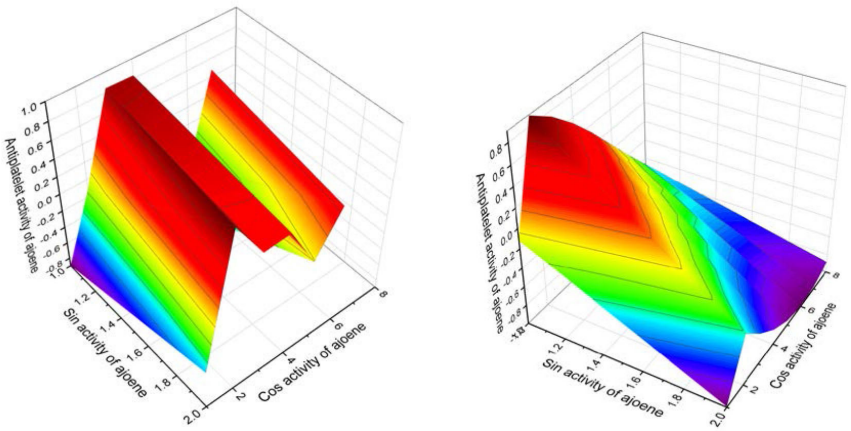

Figure 11. 3D graph shows the predicted and calculated antiplatelet activity of ajoene (**26A**, left-hand side) or (E)-1-allyl-2-(3-(allylsulfinyl)-prop-1-en-1-yl)-disulfane, with 99.7% confidence, and deoxygenated ajoene or (*E*)-1-allyl-2-(3-(allylthio)-prop-1-en-1-yl)-disulfane (**26**, right side) showing the highest degree of confidence, 99.6%.

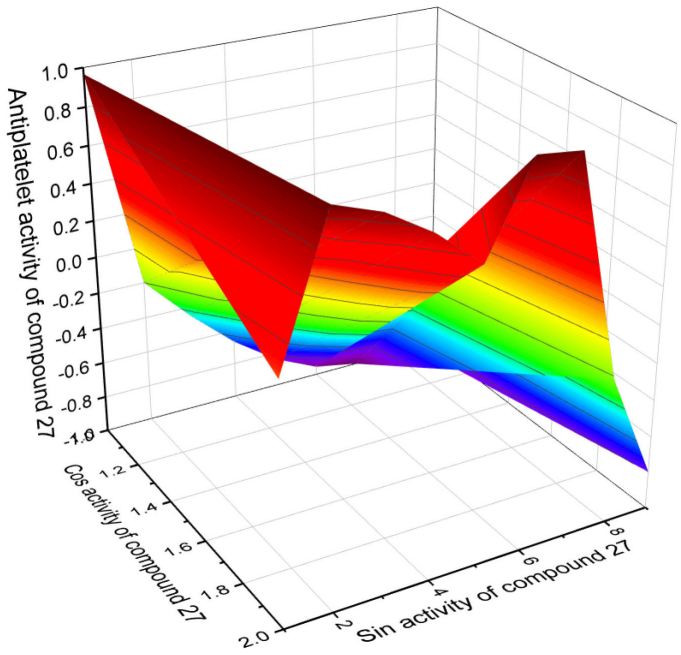

Figure 12. 3D graph shows the predicted and calculated antiplatelet activity of sulfur-containing hydrocarbon (1-((E)-but-2-en-1-yl)-2-((E)-prop-1-en-1-yl)-disulfane, **27**) showing the highest degree of confidence, 99.3%.

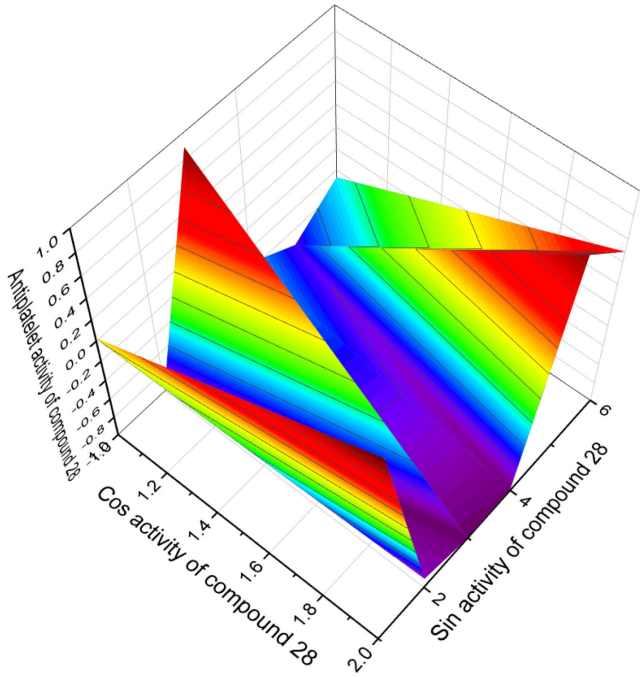

Figure 13. 3D graph shows the predicted and calculated antiplatelet activity of sulfur-containing hydrocarbon (1S,3S,5S,7S)-2,4,6-trithiaadamantane, **28**) showing the highest degree of confidence, 98.8%.

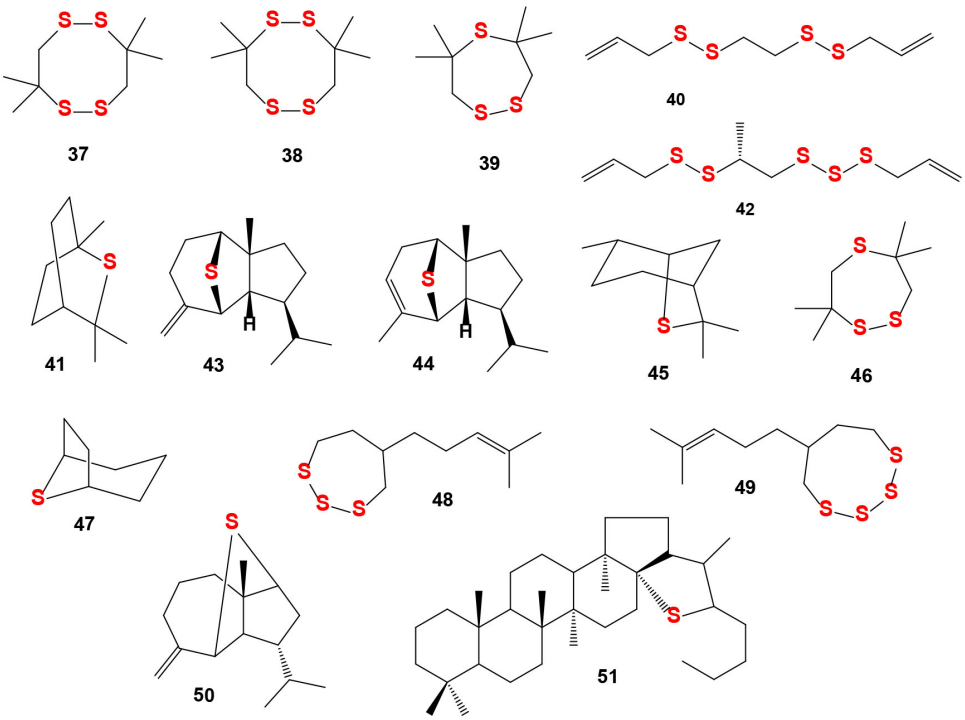

Figure 14. Natural sulfur-containing compounds as potential antiplatelet agents. The pharmacological profiles and biological activities are shown in Table 5.

hydrocarbons have higher numerical values as platelet aggregation inhibitors than compounds (**1**–**25**).

In addition, sulfur-containing hydrocarbons have a more pronounced anticoagulant effect than many of the antiplatelet agents (**7**–**25**), ticlopidine (**3**), and clopidogrel (**4**), which help prevent the formation of thrombosis. By preventing these clots, platelet antagonists help prevent heart attacks, strokes, and other heart muscle complications.

As an example, we use beraprost (**18**) as an analog of prostacyclin PGI2, which according to experimental data is a

Table 5. Pharmacological activities of natural SC hydrocarbons as potential antiplatelet drugs with low reliability from 53% to 80%.

No.	Antiplatelet and related activities (Pa)[a]	Additional predicted activities (Pa)[a]
37	Fibrinolytic (0.678)	Anti-ischemic, cerebral (0.713), chemoprotective (0.636), antiviral (arbovirus) (0.619)
		Antiviral (picornavirus) (0.600)
38	Fibrinolytic (0.678)	Anti-ischemic, cerebral (0.713), chemoprotective (0.636), antiviral (arbovirus) (0.619)
		Antiviral (picornavirus) (0.600), erythropoiesis stimulant (0.558)
39	Fibrinolytic (0.672)	Anti-ischemic, cerebral (0.691), antiviral (arbovirus) (0.630), antineoplastic (sarcoma) (0.619) Antiviral (picornavirus) (0.599), antineoplastic (renal cancer) (0.557)
		Antineoplastic (myeloid leukemia) (0.557)
40	Platelet antagonist (0.661)	Antineoplastic (myeloid leukemia) (0.955), atherosclerosis treatment (0.893)
		Prostate cancer treatment (0.725), leukopoiesis stimulant (0.665)
41	Fibrinolytic (0.660)	Antidepressant (0.865), analgesic (0.747), antiviral (arbovirus) (0.621)
		Antinephrotoxic (0.600), erythropoiesis stimulant (0.577), cardiovascular analeptic (0.570)
42	Antithrombotic (0.642)	Insulin sensitizer (0.984), atherosclerosis treatment (0.979), chemoprotective (0.951)
		Prostate cancer treatment (0.926), antineoplastic (myeloid leukemia) (0.920), antimitotic (0.892)
43	Antithrombotic (0.628)	Anti-inflammatory (0.842), prostatic (benign) hyperplasia treatment (0.783), antineoplastic (0.783)
		Atherosclerosis treatment (0.655)
44	Fibrinolytic (0.626)	Vasoprotector (0.708), atherosclerosis treatment (0.661), antineoplastic (0.661)
	Antithrombotic (0.549)	Cardiovascular analeptic (0.546)
45	Fibrinolytic (0.622)	Cardiovascular analeptic (0.615), antiviral (arbovirus) (0.566)
		Erythropoiesis stimulant (0.549), antiviral (picornavirus) (0.548)
46	Fibrinolytic (0.613)	Anti-ischemic, cerebral (0.907), leukopoiesis stimulant (0.694)
		Antiarthritic (0.598), antiviral (arbovirus) (0.561)
47	Platelet aggregation inhibitor (0.597)	Cardiotonic (0.797), antiarrhythmic (0.796)
		Antiviral (arbovirus) (0.651), antiviral (picornavirus) (0.552)
48	Antithrombotic (0.587)	Antineoplastic (0.733), apoptosis agonist (0.715), hypolipemic (0.673)
49	Antithrombotic (0.587)	Antineoplastic (0.763), apoptosis agonist (0.715), chemoprotective (0.694)
		Hypolipemic (0.673), antifungal (*Candida*) (0.660)
50	Antimetastatic (0.549)	Antineoplastic (0.782), anti-inflammatory (0.768)
	Antithrombotic (0.537)	Atherosclerosis treatment (0.551), antipruritic, allergic (0.549)
51	Antithrombotic (0.531)	Antineoplastic (0.661), anti-inflammatory (0.651)
		Cardiovascular analeptic (0.560), antimetastatic (0.546)

[a]Only activities with Pa > 0.5 are shown. Abbreviations: SC: sulfur-containing.

strong antiplatelet inhibitor, and this is confirmed in data obtained by the PASS program. Given the reliable probability that beraprost demonstrates properties as an inhibitor of platelet aggregation is 96%, the antithrombotic effect is confirmed by 92.8% (Table 2). According to PASS, sulfur-containing hydrocarbons (26-32; for structures, see Figure 4 and biological activities are shown in Table 4) demonstrate properties as an inhibitor of platelet aggregation [compound **28** (*probable confidence expressed as a percentage*) = 98.8%, **27** = 94%, and **32** = 90%]. The effect as an antagonist of platelets is **26** = 99.6%, **27** = 99.3%, **29** = 97.1%, **30** = 96.7%, and **31** = 91.6%.

Thus, the data presented using the unified PASS program of synthetic (**1–18**), natural (**19–25**), and sulfur-containing hydrocarbons (**26–51**) that are currently widely used show that sulfur-containing hydrocarbons, according to criteria determined by PASS algorithms, demonstrate different selective efficacy for the prevention or treatment of platelet dysfunction or aggregation.

CONCLUSION

Based on the data presented in this article, it was shown that well-known synthetic drugs such as aspirin, elinogrel, and beraprost, as well as natural drugs such as eptifibatide and vorapaxar, are widely used as platelet aggregation inhibitors. These drugs also show other activities such as antineoplastic, antiasthmatic, antiallergic, and antiarrhythmic activities with a high degree of confidence of over 90%. In addition, some show properties as an insulin sensitizer or can be used to treat atherosclerosis. Using the algorithms of quantitative structure–activity relationship, we conducted a detailed pharmacological analysis of the biological activities of these drugs for the treatment of platelet aggregation. This work was carried out with the aim of finding new drugs from natural sources that could supplement the arsenal of platelet aggregation inhibitors. This review is about the comparative pharmacological analysis of synthetic and natural drugs that are currently used in clinical medicine as antiplatelet

agents in comparison with natural sulfur-containing hydrocarbons that are isolated from bacteria, plant, mammalian oils, and mineral oil. The data presented may have an optimistic forecast for the sulfur-containing hydrocarbons presented in this article, since they show a high antiplatelet effect and can be promising as medicines. It can be assumed that these agents may have other mechanisms of action and fewer side effects since these compounds are relatively simple chemical structures containing only sulfur heteroatom(s).

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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