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From a Multipotent Stilbene to Soluble Epoxide Hydrolase Inhibitors with Antiproliferative Properties

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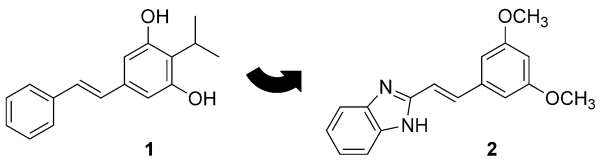
Inhibitors of soluble epoxide hydrolase (sEH) are in the focus of pharmaceutical research for numerous indications including cardiovascular disorders, diabetes and inflammatory processes.[1–5] sEH is an enzyme located in the branch of the arachidonic acid cascade that hydrolyses the epoxyeicosatrienoic acids (EETs),[6] products resulting from CYP epoxygenases, into dihydroxyeicosatrienoic acids (DHETs). Although several inhibitors reached clinical trials, the role of EETs and sEH in cancer growth and metastasis remains rather ambiguous.[7] Using genetic and pharmacological alteration of EET levels, it has been demonstrated that EETs are critical for primary tumor growth and metastasis in mouse models of cancer.[8] EETs promote metastasis by triggering secretion of the vascular endothelial growth factor (VEGF) by the endothelium, which is critical for EET cancer stimulating activity. The postulated mechanism[9] for EETs to promote tumor growth is via epidermal growth factor receptor/phosphatidylinositol 3 kinase/protein kinase B (EGFR/PI3K/Akt) and EGFR/mitogen-activated protein kinase (MAPK) pathways[10] to promote cancer cell survival. However, sorafenib,[11,12] which was originally designed as a multikinase inhibitor,[13] was found to inhibit sEH in the nanomolar concentration range, which contributes to its profile in vivo.[14,15] Looking at these studies concisely, EETs act as a double-edged sword in cancer development and treatment.

Polypharmacological compounds have gained special attention in the field of cancer treatment due to the complexity of pathways involved in cancer pathogenesis.[16–18] Natural products are one of the major sources for novel antiproliferative compounds, exhibiting various modes of cytostatic action.[19] Often natural products exhibit polypharmacological activity, targeting several pathways relevant[20] for cancer pathogenesis.[21,22] The principle of addressing multiple targets by natural products can be transferred to synthetic multitarget ligands.[23] In this study, we intended to discover chemical compounds exhibiting cytotoxic profiles and simultaneously targeting sEH. We started with a small library of compounds isolated from entomopathogenic bacteria, namely *Photorhabdus* and *Xenorhabdus*.[24] These bacteria live in symbiosis with soil-dwelling nematodes and together are able to infect and kill different insect larvae[25,26] using protein toxins but also small molecules. Key compounds required to evade the insect immune system are phenoloxidase inhibitors, with rhabduscin as the most prominent example.[27] Assuming that also other insect enzymes, like juvenile hormone epoxide hydrolase (JHEH),[28] are targeted by *Photorhabdus* and *Xenorhabdus* natural products, we analyzed our in-house compound library against the JHEH-related target sEH. We found that the pluripotent isopropylstilbene (IPS, **1**) from *Photorhabdus*[29] exhibited the desired properties by inhibiting sEH with an IC_{50} value of 10 μM (Table 1, Scheme 1).



Scheme 1. Natural product inspired design of stilbene-derived sEH inhibitors.

Stilbenes like resveratrol[30,31] or erbstatin[32] are known to possess chemopreventive or antiproliferative properties. Similarly, IPS exhibited a wide range of antiproliferative properties on different cancer cell lines, including HepG2 (hepatocarcinoma), HeLa (cervical cancer), MCF-7 (breast adenocarcinoma), A498 (renal carcinoma) and U937 (histiocytic lymphoma; Table 2).

The synthesis of IPS is not straightforward;[33] therefore, we followed the natural product inspired approach and intended to identify compounds with similar properties and simple synthetic accessibility. We screened a small collection of compounds exhibiting the stilbene scaffold (chalcones and resveratrol analogues) which was available in-house (Supporting Information, SF 3). We identified (*E*)-styryl-1*H*-benzo[*d*]imidazoles as analogues of IPS that carry a benzimidazole moiety, which was previously identified as a novel sEH pharmacophore in our

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Table 1. IC_{50} values of synthesized (*E*)-styryl-1*H*-benzo[*d*]imidazoles.[a]

Compd	R^1	R^2	R^3	IC_{50} [μM][b]	Compd	R^1	R^2	R^3	IC_{50} [μM][b]
AUDA	–	–	–	0.1 ± 0.01	**74**	3-(pyridin-3-yl)	H	H	0.8 ± 0.23
IPS (**1**)	–	–	–	10.0 ± 0.96	**75**	3-DHBD[c]	H	H	1.5 ± 0.36
3	H	H	H	5.9 ± 0.60	**31**	4-F	H	H	6.1 ± 0.45
7	2-CF_3	H	H	0.6 ± 0.13	**34**	4-CF_3	H	H	6.5 ± 0.50
10	2-NO_2	H	H	2.0 ± 0.39	**37**	4-OCH_3	H	H	7.5 ± 1.52
13	2-OCH_3	H	H	18.3 ± 1.35	**40**	4-NO_2	H	H	9.8 ± 3.94
16	2-Cl	H	H	1.7 ± 0.12	**43**	2-OCH_3	5-OCH_3	H	17.3 ± 3.11
19	2-F	H	H	2.6 ± 0.21	**46**	3-OCH_3	4-OCH_3	H	4.3 ± 0.57
22	2-Br	H	H	32.1 ± 10.10	**2**	3-OCH_3	5-OCH_3	H	5.4 ± 0.74
25	3-Cl	H	H	1.4 ± 0.11	**49**	4-Cl	2-Cl	H	9.7 ± 0.32
28	3-Br	H	H	4.3 ± 0.49	**52**	2-CF_3	H	3-F	1.9 ± 0.16
29	3-NO_2	H	H	4.6 ± 0.03	**55**	2-CF_3	H	3-CH_3	1.6 ± 0.37
30	3-OCH_3	H	H	5.8 ± 1.73	**58**	2-CF_3	H	3-Cl	2.7 ± 0.76
73	3-(furan-2-yl)	H	H	1.2 ± 0.16	**61**	2-CF_3	H	3-OCH_3	4.9 ± 1.10

[a] Structures are given in Schemes 2–3 and full chemical names can be found in the Supporting Information. [b] Data are the mean ± SD of sEH inhibition of three different experiments. IC_{50} values were determined with recombinant sEH using PHOME as substrate. [c] DHBD: 3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl).

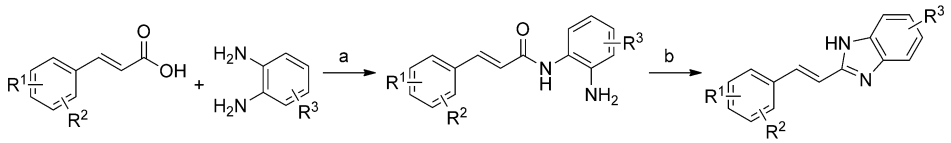
Table 2. Cell-viability EC_{50} values of selected compounds **16**, **19**, **74**, **75** and IPS (**1**) for several cancer cell lines.

Compd	EC_{50} [μM][a]				
	HepG2	HeLa	MCF-7	A498	U937
IPS (**1**)	4.7 ± 0.94	10.4 ± 2.00	ia	n.d. (73.1 % ± 14.65)[b]	2.7 ± 0.27
16	n.d. (115.1 % ± 7.21)[b]	n.d. (63.3 % ± 28.91)[b]	n.t.	n.d. (111.8 % ± 17.09)[b]	1.1 ± 0.11
19	4.7 ± 0.25	n.d. (18.0 % ± 5.20)[b]	n.t.	n.d. (96.1 % ± 19.23)[b]	2.1 ± 0.11
74	21.8 ± 5.31	18.4 ± 5.49	15.7 ± 2.43	n.d. (26.3 % ± 1.00)[b]	10.2 ± 0.23
75	21.0 ± 2.38	19.8 ± 3.03	15.1 ± 1.04	n.d. (50.7 % ± 10.42)[b]	9.2 ± 0.51

[a] All EC_{50} values were determined by at least three independent experiments using WST-1 cell viability assay and are expressed as EC_{50} ± SD. Abbreviations: n.d. = not determinable, n.t. = not tested, ia = inactive at 30 μM. [b] Cell viability [%] at 30 μM.

group.[34] The introduction of a benzimidazole does not abolish the desired antiproliferative properties, since this class of compounds showed a wide spectrum of pharmacological characteristics,[35] including antiallergic, analgesic, anti-inflammatory and antibacterial activities. Compound **2** inhibited sEH with an IC_{50} value of 5.4 μM and was used as a starting point for further optimization.

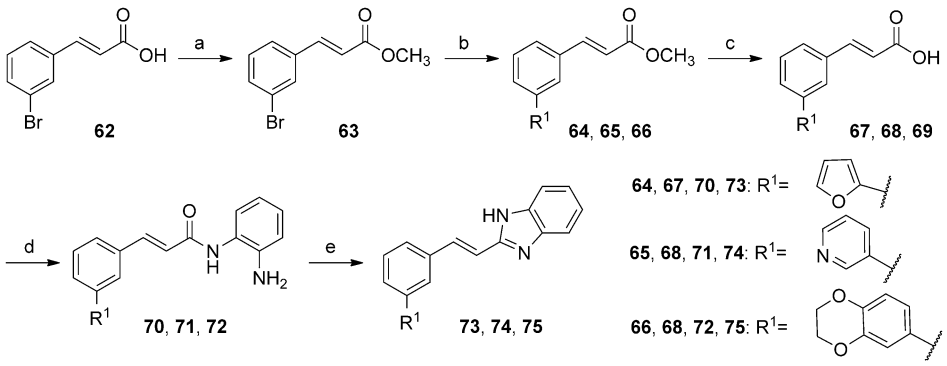
For the synthesis of a compound collection based on an (*E*)-benzimidazole stilbene scaffold, we used a previously published[36] procedure (Scheme 2) that involves the condensation of substituted *o*-phenylenediamine **5**, **50**, **53**, **56**, or **59** with the appropriately substituted (*E*)-cinnamic acid derivative **4**, **8**, **11**, **14**, **17**, **20**, **23**, **26**, **32**, **35**, **38**, **41**, **44**, or **47** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC). 4-(Dimethylamino)pyridine (DMAP) and imidazole were used as catalysts. The resulting amide intermediates **6**, **9**, **12**, **15**, **18**, **21**, **24**, **27**, **33**, **36**, **39**, **42**, **45**, **48**, **51**, **54**, **57**, and **60** were cyclized by heating under microwave irradiation in the presence of hydrochloric acid to yield the target (*E*)-styryl-1*H*-benzo[*d*]imidazoles **7**, **10**, **13**, **16**, **19**, **22**, **25**, **28**, **34**, **37**, **40**, **43**, **46**, **49**, **52**, **55**, **58**, and **61** as the corresponding hydrochloric acid salt (Scheme 2). The (*E*)-geometry of the styryl double bonds was confirmed by proton–proton coupling constants (Supporting Information, SF 1). In order to introduce an aromatic residue at the *meta* position of the phenyl ring (Scheme 3), 3-bromo-(*E*)-cinnamic acid (**62**) underwent esterification (79% yield), followed by Suzuki coupling of the key intermediate **63** with the desired aryl boronic acid (26–49% yield). After hydrolysis of **64**, **65**, and **66**, the condensation with *o*-phenylenediamine (**5**) led to amide intermediates **70**–**72**, that underwent subsequent cyclization to yield compounds **73**–**75** under microwave radiation. Compounds **3**, **29**, **30** and **31** were purchased. Inhibitory activity of styryl benzimidazole derivatives was investigated on human recombinant sEH expressed in *E. coli*[37]



4, 8, 11, 14, 17, 20, 23, 26, 32, 35, 38, 41, 44, 47 | **5, 50, 53, 56, 59** | **6, 9, 12, 15, 18, 21, 24, 27, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60** | **3, 7, 10, 13, 16, 19, 22, 25, 28, 29, 30, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61**

3*: R^1=H, R^2=R^3=H
4, **5**, **6**, **7**: R^1=2-CF_3, R^2=R^3=H
8, **9**, **10**: R^1=2-NO_2, R^2=R^3=H
11, **12**, **13**: R^1=2-OCH_3, R^2=R^3=H
14, **15**, **16**: R^1=2-Cl, R^2=R^3=H
17, **18**, **19**: R^1=2-F, R^2=R^3=H
20, **21**, **22**: R^1=2-Br, R^2=R^3=H
23, **24**, **25**: R^1=3-Cl, R^2=R^3=H
26, **27**, **28**: R^1=3-Br, R^2=R^3=H
29*: R^1=3-NO_2, R^2=R^3=H
30*: R^1=3-OCH_3, R^2=R^3=H
31*: R^1=4-F, R^2=R^3=H
32, **33**, **34**: R^1=4-CF_3, R^2=R^3=H
35, **36**, **37**: R^1=4-OCH_3, R^2=R^3=H
38, **39**, **40**: R^1=4-NO_2, R^2=R^3=H
41, **42**, **43**: R^1=2-OCH_3, R^2=5-OCH_3, R^3=H
44, **45**, **46**: R^1=3-OCH_3, R^2=4-OCH_3, R^3=H
47, **48**, **49**: R^1=4-Cl, R^2=2-Cl, R^3=H
50, **51**, **52**: R^1=2-CF_3, R^2=H, R^3=3-F
53, **54**, **55**: R^1=2-CF_3, R^2=H, R^3=3-CH_3
56, **57**, **58**: R^1=2-CF_3, R^2=H, R^3=3-Cl
59, **60**, **61**: R^1=2-CF_3, R^2=H, R^3=3-OCH_3

Scheme 2. Synthesis of (*E*)-styryl-1*H*-benzo[*d*]imidazoles. *Reagents and conditions*: a) EDC (1.5 equiv), DMAP (0.05 equiv), imidazole (0.05 equiv), RT, 4 h, 21–84%; b) 6 M aq HCl, EtOH, 120 °C, 10 min, MW, 20–92%. Compounds **3**, **29**, **30**, and **31** were purchased.



Scheme 3. Synthesis of (*E*)-styryl-1*H*-benzo[*d*]imidazoles **73**, **74** and **75** through introduction of aromatic residues at position 3. *Reagents and conditions*: a) MeOH, H_2SO_4 (0.1 equiv), reflux, 16 h, 70%; b) R^1–$B(OH)_2$ (2.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), 1 M aq Na_2CO_3, toluene/EtOH (4:1), 85 °C, 16 h, 26–49%; c) KOH (2.85 equiv), MeOH, 25 °C, 3.5 h, 64–95%; d) EDC (1.5 equiv), DMAP (0.05 equiv), *o*-phenylenediamine (1.0 equiv), imidazole (0.05 equiv), RT, 4 h, 8–32%; e) 6 M aq HCl, EtOH, 120 °C, 10 min, MW, 34–63%.

using a synthetic epoxide as a substrate (3-phenyl-cyano(6-methoxy-2-naphthalenyl)methyl ester-2-oxiraneacetic acid, PHOME).[38] As shown in Table 1, we examined the different substitutions at the phenyl ring of the styryl moiety (western part) and the substitutions at the benzimidazole scaffold (eastern part). Regarding the western part of the molecule, several compounds were synthesized bearing *ortho*, *meta* and *para* substitutions. *Ortho*-substituted compounds (**7**, **10**, **13**, **16**, **19**) yielded highest inhibitory activity, with the exception of bromo-substituted **22**. Electron-donating groups like methoxy (compound **13**) were less tolerated (IC_{50} = 18.3 μM), and the best inhibition was obtained with trifluoromethyl-substituted compound **7** (IC_{50} = 0.6 μM). Unsubstituted compound **3** resulted in a 10-fold loss of potency compared with the best compound **7**. With the exception of bromo-substituted **22** (IC_{50} = 32.1 μM), halogen groups in the *ortho* position exhibited moderate inhibition with IC_{50} values in the range of 1.7 to 2.6 μM .

Lower inhibitory activity was observed for **29** and **30**, indicating that *meta* substitution is less favored than *ortho* substitution. However, we confirmed the tendency concerning the electron-donating properties of the substituent, as compound **30** decreases the inhibitory activity (IC_{50} = 5.8 μM). The introduction of heterocyclic moieties, such as furane (**73**), pyridine (**74**) or 2,3-dihydrobenzo[*b*][1,4]dioxine (**75**), increased the inhibitory potency (**73**: IC_{50} = 1.2 μM, **74**: IC_{50} = 0.8 μM, **75**: IC_{50} = 1.5 μM, Table 1). In contrast to the positive substituent effect observed for *ortho*-substituted compounds, *para*-substitution pattern resulted in a weaker inhibitory activity regardless of the electron-donating nature of the substituent.

Additionally, double substitution at the phenyl moiety was explored and led to a decrease in the inhibitory activity. 2,5-Methoxy-substituted compound **43** (IC_{50} = 17.3 μM) exhibited the lowest inhibitory activity, which could be restored by a 3,4-dimethoxy (**46**, IC_{50} = 4.3 μM) or 3,5-dimethoxy substitution pattern (**2**, IC_{50} = 5.2 μM). The potency was not completely restored by exchanging the methoxy groups to a 3,4-dichloro pattern (**49**, IC_{50} = 9.7 μM).

After exploring the phenyl moiety, we could conclude that the best substitution pattern was *ortho*-trifluoromethyl (compound **7**, IC_{50} = 0.6 μM). Therefore, derivatives of compounds bearing altered eastern substitution were synthetized. Electron-donating groups as in methoxy-substituted **61** (IC_{50} = 4.9 μM) exhibited inhibitory activity; however, **52** (IC_{50} = 1.9 μM), **55** (IC_{50} = 1.6 μM) and **58** (IC_{50} = 2.7 μM) bearing electron-withdrawing groups partially restored the activity.

The structure–activity relationship (SAR) of the investigated styryl benzimidazoles on sEH are rather flat, which correlates with the possible binding mode proposed by the molecular docking experiment of the most potent compound **7** (Figure 1, see the Supporting Information for details). Both nitrogen atoms of the benzimidazole core seem to interact with the catalytic center of sEH (Tyr381, Asp333, Tyr465). The largest part of the benzimidazole scaffold is enclosed in the Trp334 niche (15 Å) capable for aryl interactions. The phenyl moiety showed π-stacking with Met419[39] and His524, and the benzimidazole core showed π-stacking with Trp334. The additional space around both aromatic cores correlates with the high tolerability of different substituents, as demonstrated by the SAR.

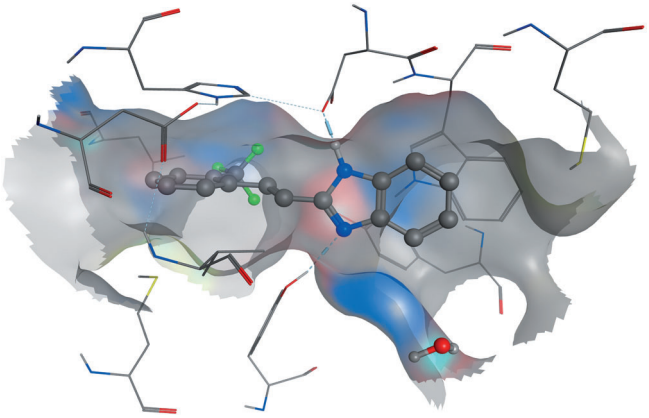


Figure 1. Docking pose of (*E*)-styryl-1*H*-benzo[*d*]imidazole **7** in the binding pocket of the catalytic domain of sEH (PDB: 3KOO).

We evaluated the effect of compounds IPS (**1**; IC_{50} = 10.0 μM), **16** (IC_{50} = 1.7 μM), **19** (IC_{50} = 2.6 μM), **74** (IC_{50} = 1.2 μM) and **75** (IC_{50} = 0.8 μM) on cell viability of several cancer lines (Table 2). IPS inhibited the proliferation activity of all cell lines except MCF-7. In the water-soluble tetrazolium salt (WST-1) assay, EC_{50} values were in the range of 2.7 to 10.4 μM. *Ortho*-substituted compounds **16** and **19** affected the proliferation

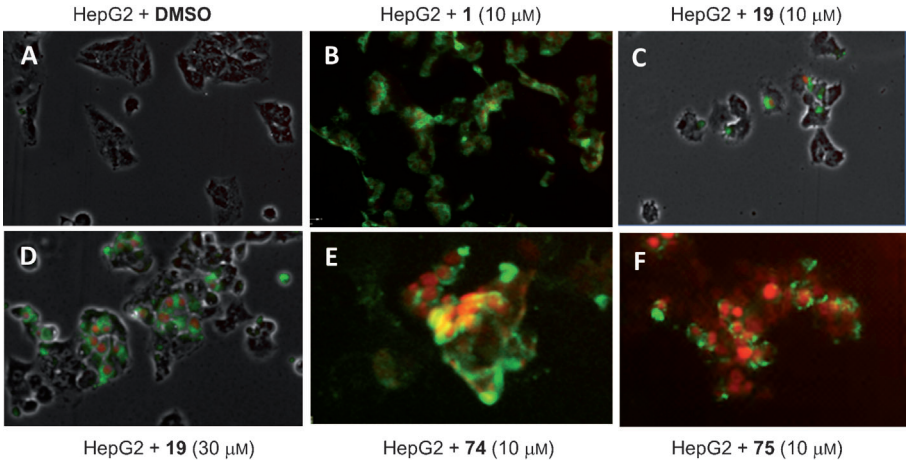


Figure 2. Annexin V/PI staining of HepG2 cells incubated with A) 1% DMSO for 48 h, B) **1** (10 μM) for 24 h, C) **19** (10 μM) for 48 h, D) **19** (30 μM) for 48 h, E) **74** (10 μM) for 24 h, F) **75** (10 μM) for 24 h.

activity of HeLa and U937 (suspension cells). *Ortho*-fluoro-substituted compound **19** inhibited cell proliferation of HepG2 (EC_{50} = 4.7 μM) and U937 (EC_{50} = 2.1 μM) and slightly of HeLa cells (30 μM, 18%).

Compounds **74** and **75** affected the cell growth of the different cancer cell lines to a lesser extent. Compound **74** inhibited the growth of HepG2 (EC_{50} = 21.8 μM), HeLa (EC_{50} = 18.4 μM), MCF-7 (EC_{50} = 15.7 μM), U937 (EC_{50} = 10.2 μM), and to some extent A498 cell lines (resulting in only 26% cell viability at 30 μM). Similarly, compound **75** displayed inhibitory activity on all cancer cell lines. EC_{50} values ranged from 9.2 to 21.5 μM (Table 2). Interestingly all compounds inhibited the cell proliferation of suspension cells U937.

In order to distinguish between an apoptotic or necrotic mechanism, we stained HepG2 cells after treatment with compounds **19**, **74** and **75** during 24–48 h with annexin V/propidium iodide (PI; Figure 2). Cells treated with **19** clearly showed apoptosis in a concentration-dependent manner compared to vehicle (dimethyl sulfoxide) after staining. With compound **74** cells showed progressing apoptosis, whereas cells treated with **75** showed a more late apoptotic/necrotic phenotype over the same time course. IPS (**1**)-treated cells were clearly early apoptotic.

In conclusion, inspired by the initial hit compound, IPS, a series of (*E*)-styryl-1*H*-benzo[*d*]imidazole derivatives were synthesized and evaluated with recombinant sEH, which led to potent sEH inhibitors exhibiting antiproliferative activities. Although the benzimidazole stilbenes presented in this work do not reach the picomolar potencies of urea-based sEH inhibitors,[3] they represent an unprecedented scaffold for further development. Following the approach of natural product inspired design recently proposed by Waldmann et al.,[40] we were able to transfer and even enhance the desired biological activity from a bacterial secondary metabolite to a synthetic compound series. The resulting compounds are accessible via a facile synthetic route and offer the possibility to investigate structure–activity relationships. The natural product inspired drug design extends the valuable role of natural products as drugs and drug precursors to templates for fully synthetic bioactive molecules.

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Keywords: benzimidazoles · cancer · polypharmacology · soluble epoxide hydrolase · stilbenes

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