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*Article*

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# Isolation and *in silico* SARS-CoV-2 main protease inhibition potential of chrysoeriol from *Chondrilla brevirostris* Fisch. & C.A. Mey.

The genus *Chondrilla* L. comprises 22 species on the CIS territory. 16 species of them grow in Kazakhstan. All species of the genus *Chondrilla* L. are rubber-bearing herbaceous plants that belong to the *Asteraceae* family. We picked *Chondrilla brevirostris* Fisch. & C.A. Mey. for the chemical study. It is a perennial herb that grows in desert steppes and forest meadows. The aboveground parts of *Ch. brevirostris* were extracted with ethanol at room temperature. Several fractions were obtained by separating ethanol extract on column chromatography. Rechromatography and preparative thin-layer chromatography were used to further study the obtained fractions and the isolation of flavonoids. As a result of preparative thin-layer chromatography, the flavonoid 5,7,4'-trihydroxy-3'-methoxyflavone (compound **1**) was isolated. The chemical structure of **1** was established by spectroscopic data. Compound **1** was isolated for the first time from the species of *Chondrilla*. Compound **1** was subjected to a molecular docking study against COVID–19 main protease ($M^{pro}$) to investigate its expected activity against SARS-CoV-2. In this case, the substance showed a good binding mode with a free energy of –6.22 kcal/mol, while the binding energy of the co-crystallized ligand was –7.83 kcal/mol.

*Keywords*: *Chondrilla brevirostris*, Asteraceae, extraction, column chromatography, PTLC, isolation, flavonoid, structure, spectroscopy, molecular docking study.

## *Introduction*

*Chondrilla* L. is a genus of plants in the *Asteraceae* family. *Chondrilla brevirostris* Fisch. & C.A. Mey. is the most well-known species from this genus. It widely grows in Kazakhstan, China, Kyrgyzstan and Russia. Synonyms of the plant are *Chondrilla filifolia* Iljin and *Chondrilla juncea* Ledeb. [1].

Previously, four flavonoids, including luteolin, luteolin-7-glucoside, luteolin-7-galactosylglucuronide and quercetin-3-galactoside, were reported from this plant [2].

Plant material is still important in finding new and bioactive compounds that are of practical interest as a source of new drugs. This indicates the relevance of this research. This work aims to isolate and identify, as well as to study the molecular docking of the isolated flavonoid from a plant source.

Recently, several scientific records reported the use of molecular docking studies to prove the biological activities of natural compounds [3–6]. Accordingly, we applied the isolated compound to *in silico* studies aiming at exploring its biological importance.

## *Experimental*

*General experimental procedures*. Column chromatography separations (CC) were performed on glass columns packed with silica gel (230–400 mesh ASTM, Merck, LTD, Japan). Thin layer chromatography (analytical and preparative thin layer chromatography (TLC) was performed on silica gel 60 F 254 Glass plates (Merck, LTD, Japan). Spots were visualized under a UV light (254 and 366 nm) and by spraying with 10 % sulfuric acid reagent followed by heating. Isolated compound was identified by NMR analysis ($^1$H 500 MHz) acquired on the Jeol Delta. TMS was an internal standard. DMSO-$d_6$ was a solvent. Coupling constants are given in Hertz. The chemical shifts are expressed in δ ppm.

*Plant Material*. The aerial parts of *Ch. brevirostris* were collected in the steppe, 200 km from Zhezkazgan city, Kazakhstan, in August 2019, stage flowering — fruiting. The plant material was examined by Professor M. Ishmuratova, Department of Botany, Karagandy University of the name of academician E.A. Buketov (Republic of Kazakhstan), and classified as belonging to the *Ch. brevirostris* group and deposited in the herbarium of the faculty of biology and geography.

*Extraction and Isolation*. Dry finely ground raw materials (aboveground part) of *Ch. brevirostris* (1.0 kg) were extracted three times with ethanol by standing for 1 day at room temperature. The ethanol extracts were combined and evaporated under reduced pressure to yield a crude extract of 68 g. Chromatographic separation of the crude extract was carried out on a silica gel column using the system hexane — acetone with a gradient increase of the latter and then with methanol. The fractions were studied on TLC, and similar fractions were combined. Compound (**1**) (4 mg) was separated by using PTLC in the system of chloroform-methanol (200+10 mL).

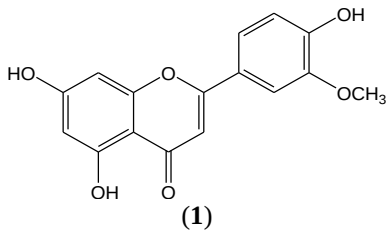
*Compound identification*. *5,7,4'-Trihydroxy-3'-methoxyflavone (chrysoeriol)* (**1**) [7]: Pale yellow powder, $C_{16}H_{12}O_6$, Yield is 4 mg. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ (ppm): 12.97 (s, 5-OH), 6.87 (s, H-3), 6.15 (d, *J* =2.0 Hz, H-6), 6.46 (d, *J* =2.0 Hz, H-8), 7.55 (d, *J* =2.0 Hz, H-2'), 6.92 (d, *J* =9.0 Hz, H-5'), 7.55 (dd, *J* = 2.0, 9.0 Hz, H-6'), 3.89 (s, 3'-$OCH_3$).

*Molecular docking study*. The crystal structures of the target enzymes COVID–19 main protease ($M^{pro}$) (PDB ID: 6lu7, resolution: 2.16 Å) were downloaded from Protein Data Bank (http://www.pdb.org). Molecular Operating Environment (MOE) was used for the docking analysis [8, 9]. The free energies and binding modes of the examined molecules against $M^{pro}$ were determined. At first, water molecules were removed from the crystal structure of $M^{pro}$, retaining only one chain, which was essential for binding. The Co-crystallized ligand (PRD-002214) was used as a reference ligand. Then, the protein structure was protonated and the hydrogen atoms were hidden. Next, the energy was minimized and the binding pocket of the protein was determined [10, 11].

The structure of the examined compound and the co-crystallized ligand were drawn using Chem Bio Draw Ultra 14.0 and saved as SDF format. Then, the saved file was opened using MOE software and 3D structures were protonated. Next, the energy of the molecules was minimized. A validation process was performed for the target receptor by running the docking process for only the co-crystallized ligand. Low RMSD values between docked and crystal conformations indicated valid performance. The docking procedures were carried out utilizing a default protocol. In each case, 30 docked structures were generated using genetic algorithm searches. The output from MOE software was analyzed further and visualized using Discovery Studio 4.0 software [12, 13].

## *Results and Discussion*

The aerial parts of *Ch. brevirostris* were extracted with ethanol. The EtOH solutions were combined and evaporated under reduced pressure. As a result of chromatography (rechromatography, PTLC), a pale yellow powder (**1**) was obtained. The yield was 4 mg. Analysis of spectral ($^1$H NMR) characteristics suggested that the isolated substance (**1**) was flavonoid chrysoeriol (5,7,4'-Trihydroxy-3'-methoxyflavone).




(**1**)

The compound (**1**) structure was established based on $^1$H NMR spectrum data. Characteristic proton signal at C-3 was detected in the form of a singlet at 6.87 ppm. Proton signals at C-6 and C-8 resonate as doublets at 6.15 and 6.46 ppm, respectively, with J=2 Hz. Proton signals at C-2' and C-5' appear in the form of doublets in the area of 7.55 and 6.92 ppm with J=2 and J=9 Hz, respectively. A proton signal appears in the form of a doublet-doublets at 7.55 ppm with the J=9 Hz. The signal of protons of the methoxy group appears in the spectrum at 3.89 ppm in the form of a singlet. The presence of a hydroxyl group at C-5 is confirmed by the presence of a single-proton singlet signal in the $^1$H NMR spectra spectrum at 12.97 ppm.

A docking study was carried out for compound (**1**) against the COVID–19 main protease ($M^{pro}$) (PDB ID: 6lu7, resolution: 2.16 Å) to examine the mode of binding with the proposed target. The co-crystallized ligand (PRD-002214) was used as a reference molecule. The docking studies revealed that the docked compound had good binding affinities against COVID–19 main protease with binding free energies.

The crystallized ligand (PRD-002214) showed binding energy of -7.83 kcal/mol. The detailed binding mode of the crystallized ligand was as follows: The 2-oxopyrrolidin-3-yl moiety occupied the first pocket of $M^{pro}$, forming three hydrogen bonds with Phe140, His163, and Glu166. Additionally, *tert*-butyl carbamate moiety occupied the second pocket of $M^{pro}$. Furthermore, the phenyl ring of phenylalanine moiety occupied the third pocket of the receptor forming hydrophobic interaction with His41. Moreover, ethyl propionate moiety was incorporated in the fourth pocket (Figures 1–3).

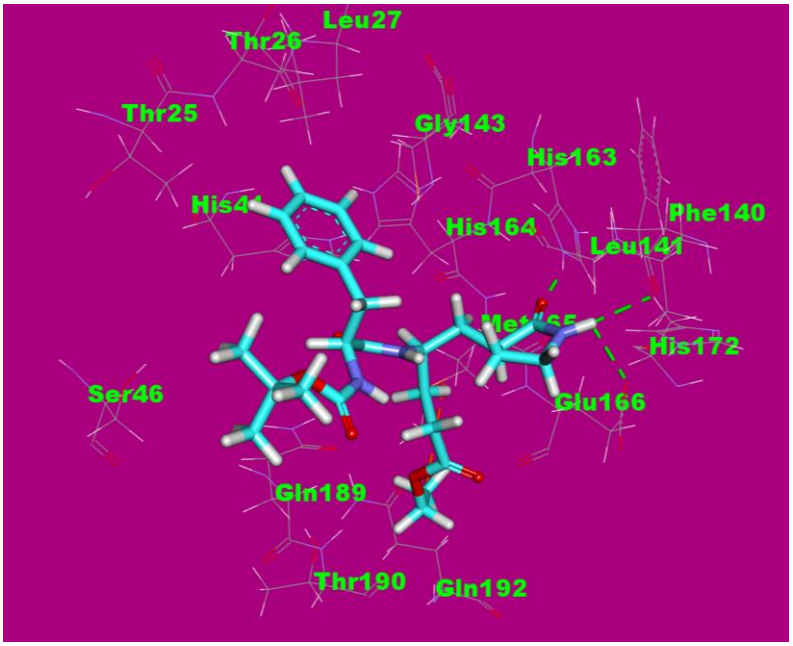



Figure 1. Co-crystallized ligand (*PRD-002214*) docked into the active site of the COVID–19 main protease, the hydrogen bonds are represented in green dashed lines and the hydrophobic interactions are represented in orange dashed lines

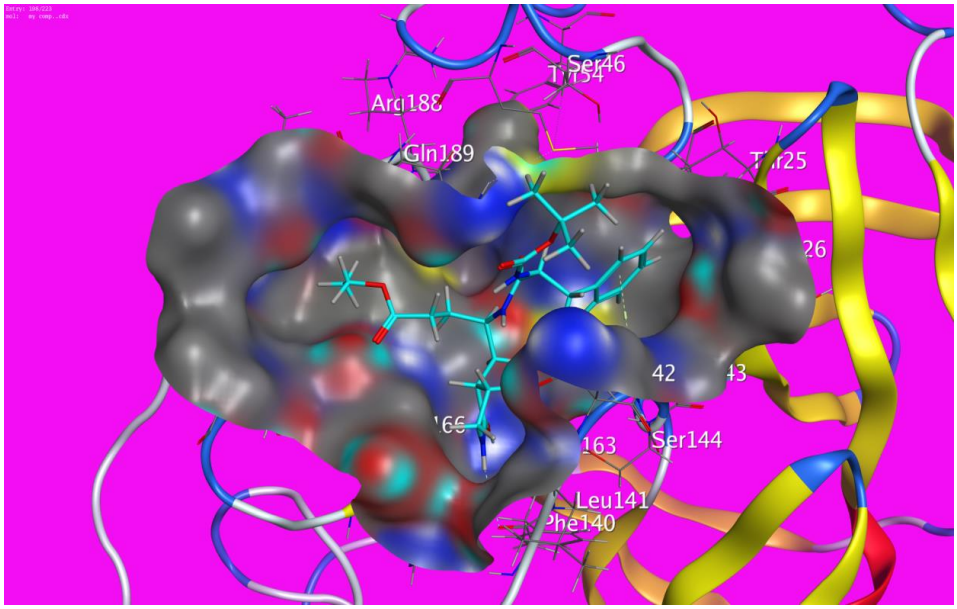



Figure 2. Mapping surface showing the co-crystallized ligand (PRD-002214) occupying the active pocket of the COVID–19 main protease

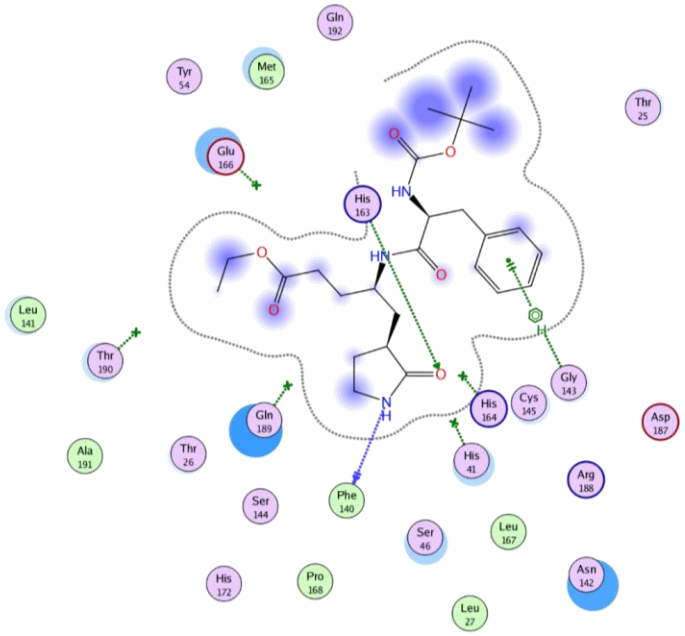



Figure 3. 2D interaction of the co-crystallized ligand (PRD-002214)
in the active site of the COVID–19 main protease

Compound (**1**) showed good binding mode with energy of –6.22 kcal/mol (Tab. 1) occupying three pockets of $M^{pro}$. The detailed binding mode was as follows: The 2-methoxyphenol moiety occupied the first pocket of $M^{pro}$ forming two hydrogen bonds with Gly143 and Leu141. Additionally, it showed one electrostatic attraction with Cys145. The 4H-pyran-4-one moiety occupied the second pocket of $M^{pro}$ forming one hydrophobic interaction with Met165. Furthermore, the 1,3-dihydroxybenzen moiety occupied the third pocket of the receptor forming one hydrogen bond with Gln192 (Figures 4–6).

Table 1

**The docking binding free energies of compounds, simeprevir and the co-crystallized ligand (PRD-002214) against COVID–19 main protease**

| Compounds | Binding free energy (kcal/mol) |
|---|---|
| (**1**) | –6.19 |
| Co-crystallized ligand (PRD-002214) | –7.83 |

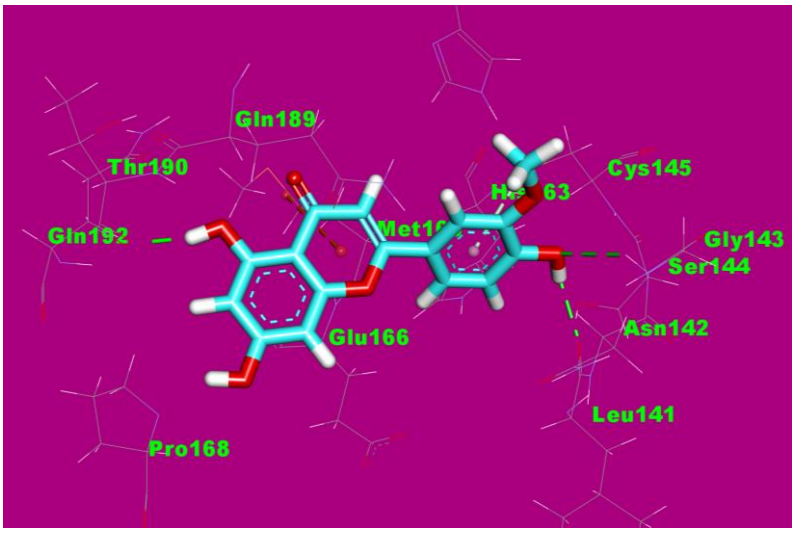



Figure 4. Compound **1** docked into the active site of the COVID-19 main protease, the hydrogen bonds are represented in green dashed lines and the hydrophobic interactions are represented in orange dashed lines

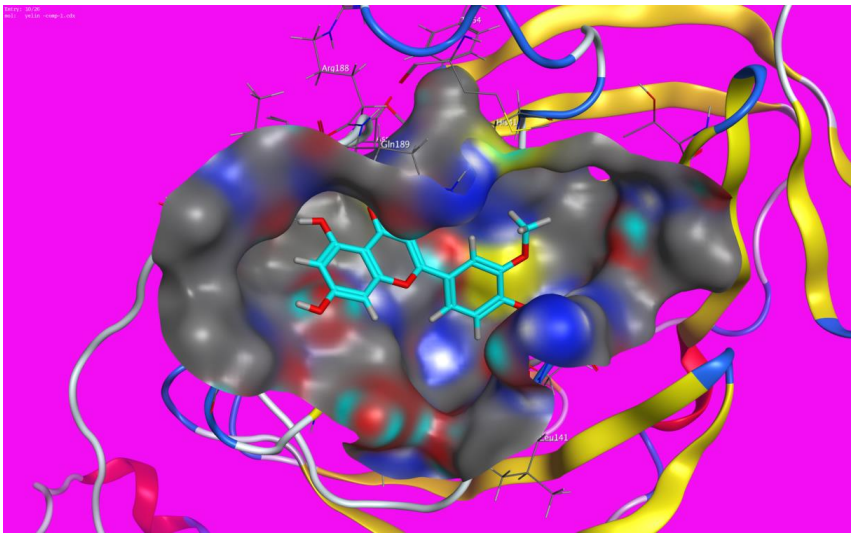



Figure 5. Mapping surface showing compound **1** occupying the active pocket of the COVID-19 main protease

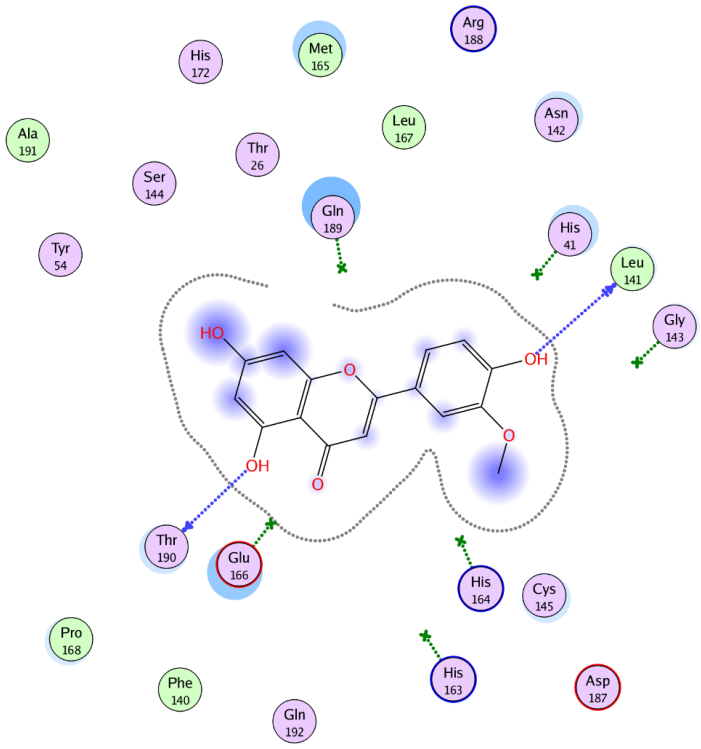



Figure 6. 2D interaction of compound **1** in the active site of the COVID–19 main protease

## *Conclusions*

By virtue of the column chromatography, then by preparative thin-layer chromatography of the extract obtained from ethanol extraction of the aboveground parts of *Chondrilla brevirostris* Fisch. & C.A. Mey., the flavonoid 5,7,4'-trihydroxy-3'-methoxyflavone was isolated. This compound from *Ch. brevirostris* was isolated for the first time. *In silico*, molecular docking study was carried out for the isolated compound against the COVID–19 main protease. As a result, the compound showed good binding energy.

## *Acknowledgments*

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## *Chondrilla brevirostris* Fisch & C.A. Mey-ден хризоэриолдың бөліп алынуы және *in silico* SARS-CoV-2 негізгі протеазаны ингибирлеу потенциалы

*Chondrilla* L. туысының ТМД аумағында 22 түрі бар, олардың 16–сы Қазақстанда. *Chondrilla* L. туысының барлық түрлері — сағызды өсімдік, күрделі гүлділер (*Asteraceae*) тұқымдасына жататын шөптесін өсімдіктер. Химиялық зерттеу үшін *Chondrilla brevirostris* Fisch & C.A. Mey. алынды. Бұл шөлді дала мен орман шалғындарында өсетін көпжылдық шөпті өсімдік. *Ch. brevirostris*-тің өсімдік шикізатын зерттеу үшін 2019 жылдың тамыз айында Қарағанды облысының Жезқазған қаласынан 200 шақырым жерде гүлдену мен жеміс беру кезеңінде жиналды. *Ch. Brevirostris* жер үсті бөлігі бөлме температурасында этанолмен экстракцияланды. Этанол сығындысын колонкалық хроматография арқылы бөлу нәтижесінде бірнеше фракциялар алынды. Алынған фракцияларды әрі қарай зерттеу және флавоноидтарды бөліп алу үшін рехроматография және препаративті жұқа қабатты

хроматография қолданылды. Препаративті жұқа қабатты хроматографиялау нәтижесінде флавоноид 5,7,4'-тригидрокси-3'-метоксифлавон (қосылыс 1) бөлінді. Қосылыстың 1 химиялық құрылымы спектроскопиялық мәліметтер бойынша дәлелденді. Бұл қосылыс *Chondrilla*-ның осы түрінен алғаш рет бөлініп алынды. Бөлініп алынған қосылысқа докинг зерттеулері жүргізілді. Бұл жағдайда қосылыс жақсы байланыс энергиясын –6,22 ккал/моль көрсетті, ал эталондық молекуланың байланыс энергиясы –7,83 ккал / мольді құрады.

*Кілт сөздер: Chondrilla brevirostris, Asteraceae*, экстракция, колонкалық хроматография, ПЖҚХ, оқшаулау, флавоноид, құрылым, спектроскопия, докинг зерттеуі.

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# Выделение и *in silico* основной потенциал ингибирования протеазы SARS-CoV-2 хризоэриола из *Chondrilla brevirostris* Fisch. & C.A. Mey

Род *Chondrilla* L. на территории СНГ насчитывается 22 вида, из них 16 — в Казахстане. Все виды рода *Chondrilla* L. являются каучуконосными растениями, родом травянистых растений семейства сложноцветных (*Asteraceae*). Для химического исследования использовано *Chondrilla brevirostris* Fisch. & C.A. Mey., представляющее многолетнее травянистое растение, произрастающее в пустынных степях и на лесных лугах. Растительное сырье *Ch. Brevirostris* для исследований было собрано в августе 2019 года в 200 км от г. Жезказгана Карагандинской области в фазе цветения–плодоношения. Надземную часть *Ch. brevirostris* экстрагировали этанолом при комнатной температуре. В результате разделения этанольного экстракта на колоночной хроматографии было получено несколько фракций. Для дальнейшего изучения полученных фракций и выделения флавоноидов применяли рехроматографию и препаративную тонкослойную хроматографию. В результате препаративной тонкослойной хроматографии был выделен флавоноид 5,7,4'-тригидрокси-3'-метоксифлавон (соединение 1). Химическая структура 1 была установлена по спектральным данным. Данный флавоноид из этого вида *Chondrilla* был выделен впервые. Оно было подвергнуто докинг исследованию. При этом вещество показало хорошую энергию связи –6,22 ккал/моль, а энергия связи эталонной молекулы составила –7,83 ккал/моль.

*Ключевые слова*: *Chondrilla brevirostris, Asteraceae*, экстракция, колоночная хроматография, ПТСХ, выделение, флавоноид, структура, спектроскопия, докинг исследование.

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