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On the pairwise cocrystallization of racemic compounds

Fuli Zhou, Carole Body, Koen Robeyns, Tom Leyssens, and Oleksii Shemchuk*

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In the field of crystallization-based chiral resolution, preferential crystallization is particularly interesting. In recent work, we showed how the simultaneous resolution of two racemic compounds can be realized through the formation of chiral conglomerate cocrystals. The crystallization of a compound as a conglomerate is a rather rare phenomenon. In this study, we decided to test the probability of multi-component conglomerate formation between two racemic compounds by cocrystallizing racemic compounds with each other. Specifically, racemic proline, mandelic acid and etiracetam were cocrystallized with 14 racemic coformers. The analysis of XRPD patterns upon grinding revealed 16 potential cocrystals, four of which have been already published. The crystal structures of all new cocrystals were determined by single crystal diffraction. The crystal structure elucidation showed 13 cocrystals were racemates and 3 were conglomerates. All conglomerates are isomorphous as they were formed between etiracetam and mandelic acid or its 2-fluoro- and 2-chloro-derivatives. Simultaneous resolution through preferential cocrystallization of racemic compounds, therefore, is limited to very specific systems. In parallel, our results did, however, highlight a striking success rate of DL-proline in the context of cocrystallization as 11 out of 14 cocrystallization experiments were successful.

Introduction

Enantiomers are mirror-image isomers showing identical physicochemical properties but different biological activities.[1] The majority (56%) of active pharmaceutical ingredients (APIs) currently available on the drug market have a chiral centre. Around 80% of them are formulated as racemic mixtures.[2] As enantiomers of a chiral biologically active compound typically exhibit different pharmacological activities, regulatory agencies advise marketing only the therapeutically active isomer.[3] Consequently, pharmaceutical companies prefer to switch to developing single enantiomer drug products[4] and in 2015, 94% of the newly marketed drug-like compounds with a chiral centre were enantiopure.[5]

Enantiomerically pure compounds can be obtained by either asymmetric synthesis or chiral resolution[6] – the separation of mixtures of enantiomers. Despite remarkable progress in the field of asymmetric synthesis,[7-10] it still suffers limitations with feasibility and cost-efficiency being typically the most significant concerns. Therefore, developing novel resolution methodologies for racemates remains a very important and contemporary topic of research. In this context, crystallization-based technologies are most commonly used due to their advantages in economic consumption capacity, manufactural reliability, and method universality.

The types of crystallization-based technologies that can be used depend on the nature of the solid. For racemic compounds, a resolution agent is typically required, whereas for conglomerates separation already occurs for the native solid. For these latter systems, preferential crystallization can be used to resolve enantiomers.[11, 12] However, statistically only 5-10% of chiral compounds form stable conglomerates.[13]

To tackle this issue, crystal engineering[14] approaches can be used to transform racemic compounds into conglomerates. To this end, cocrystallization[15-21] has recently emerged as a viable tool.[22-24] Cocrystallization with achiral coformers has proven to be useful to transform a racemic compound into a conglomerate[25-27], a result which was then used to develop resolution through preferential cocrystallization.[25, 26] We, recently, extended this approach, focusing not on an achiral counterpart but a racemic one, showing the potential to simultaneously resolve two racemic compounds through preferential cocrystallization.[28] The cocrystallization of RS-mandelic acid with RS-etiracetam, indeed, leads to the formation of a stable R-mandelic acid-R-etiracetam, S-mandelic acid-S-etiracetam cocrystal conglomerate, and, subsequently, a process allowing simultaneous chiral resolution of two racemates by preferential cocrystallization was developed.[28]

Inspired by these results, we decided to perform a more thorough investigation of cocrystallization between two racemic compounds, to grasp whether conglomerate formation between two racemic compounds is generally observed or rather an exceptional finding. To do so, we decided to focus our attention on three racemic target compounds, RS-etiracetam, RS-mandelic acid and DL-proline, which were cocrystallized with each other as well as 12 racemic counter-compounds (Scheme 1). The cocrystallization outcomes were analysed via powder and single crystal X-ray diffraction.

Institute of Condensed Matter and Nanosciences, Université Catholique de Louvain, Louvain-La-Neuve, Belgium.

† Footnotes relating to the title and/or authors should appear here.

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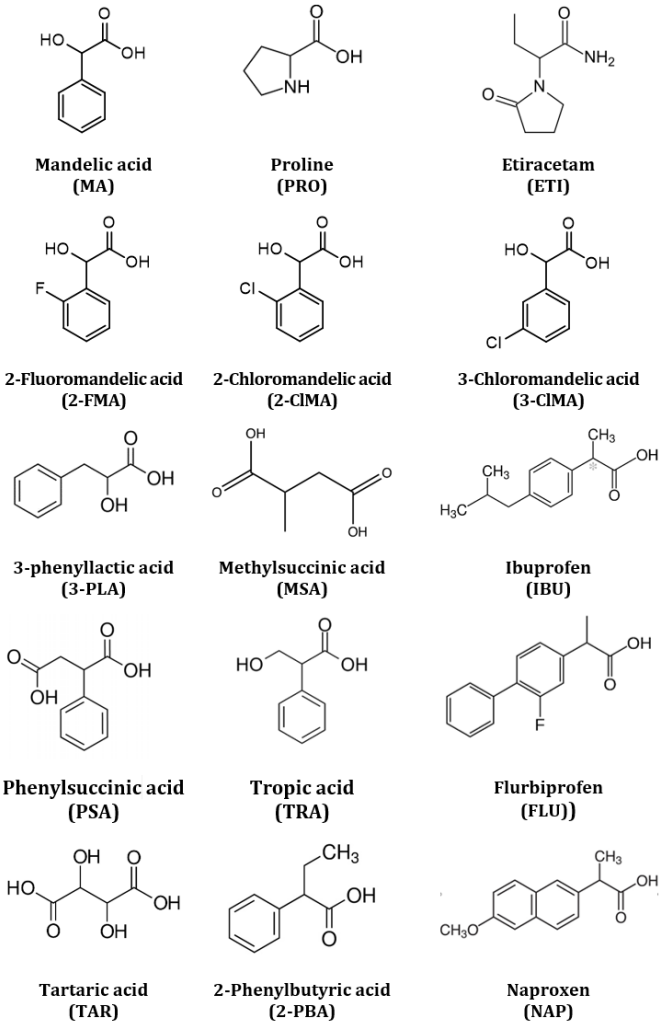

Scheme 1. Chemical structures of the investigated racemic compounds.

Experimental

Materials

RS-2-phenylbutyric acid and RS-ibuprofen were purchased from Aldrich Co. Ltd. DL-3-phenyllactic acid, DL-mandelic acid, DL-tartaric acid, DL-phenylsuccinic acid, and DL-tropic acid were purchased from Acros Co. Ltd. RS-methylsuccinic acid and RS-flurbiprofen were purchased from TCI Co. Ltd. RS-naproxen was purchased from Sigma Co. Ltd. RS-3-chloromandelic acid and RS-2-chloromandelic acid were purchased from Alfa Aesar Co. Ltd. (RS)-2-fluoromandelic acid was purchased from Fluorochem. Co. Ltd. DL-proline was purchased from Roth. Co. Ltd. RS-etiracetam was synthesized by racemizing enantiopure S-2-(2-oxopyrrolidin-1-yl) butanamide.[29]

Cocrystal screening

Cocrystal screening was performed by neat grinding, using a "Retsch Mixer Mill MM 400" equipped with two grinding jars containing five Eppendorf tubes of 2 mL each. Each tube was filled with an equimolar amount of the reagents for a total of about 100mg of material and two Ø 3 mm stainless-steel beads. Grinding was then performed at 30 Hz for 90 minutes.

Powder X-ray Diffraction (XRPD)

For phase identification purposes, X-ray powder diffraction (XRPD) patterns were collected on a PANalytical Bragg-Brentano diffractometer, using Ni-filtered CuKα (λ = 1.54179 Å) at 45 kV and 30 mA with an X'Celerator detector. Each sample was analysed in the 4 - 40° 2θ range with a step size of ca. 0.0167° and a total scan time of 6min42s.

Alternatively, XRPD measurements were performed with a Siemens D5000 diffractometer equipped with a Cu X-ray source operating at 40kV and 40 mA and a secondary monochromator allowing selection of the Kα radiation of Cu (λ = 1.5418 Å). A scanning range of 2θ values from 5° to 50° at a scan rate of 0.6° min^{-1} was applied.

The experimentally obtained XRPD patterns were compared with the corresponding starting materials and, whenever applicable, with the simulated XRPD patterns from the corresponding single crystal structures (Fig. ESI-12-26).

Single Crystal Synthesis

All single-crystals described in this work were prepared by recrystallization of the cocrystals obtained by grinding experiments. The powders were divided into three parts and dissolved in methanol, acetonitrile, and acetone and the solutions were left to evaporate at room temperature. Single crystals suitable for X-ray diffraction analyses were usually obtained in 2-10 days.

Single Crystal X-ray Diffraction

Single crystal X-ray diffraction was performed on a MAR345 image plate using monochromated Mo Kα radiation (λ = 0.71073 Å) (Montel mirror) produced by an Incoatec microfocus source. The structures were solved by dual-space direct methods (SHELXT), and refined against $|F^2|$ using SHELXL-2018/3. Crystallographic data and structure refinement details for all crystal structures discussed herein are reported in Tables ESI-1-3.

CCDC numbers 2247553-2247569 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Results and discussion

The cocrystallization experiments between racemic compounds were performed mechanochemically, by neat grinding. The potential outcomes of a cocrystal experiment between two racemic compounds are shown in Scheme 2. The cocrystallization might lead to the formation of a full racemic cocrystal (Eq. 1) or to the physical mixture of the racemates (racemic compounds are more stable than potential cocrystal – Eq. 2). A third potential outcome is the formation of stable conglomerates according to Eq. 3 and 4. Initial neat grinding experiments (Table 1) allowed identifying those situations for which a physical mixture of racemates was obtained (Eq.2), and those for which cocrystallization occurred. For the latter, the reaction occurs either through Eqs. 1, 3 or 4. As multiple outcomes are possible, for these experiments single crystals were grown and analysed by X-ray diffraction to identify which combination was formed. At that point the simulated XRPD

patterns were compared with the grinding outcome to confirm the single crystal solid-state matched that of the grinding experiment.

$R_1S_1 + R_2S_2 \rightarrow R_1S_1{\cdot}R_2S_2$ **(Eq. 1)**

$R_1S_1 + R_2S_2 \rightarrow$ **physical mixture of racemates** **(Eq. 2)**

$R_1S_1 + R_2S_2 \rightarrow R_1R_2 + S_1S_2$ **or** $R_1S_2 + S_1R_2$ **(Eq. 3)**

$R_1S_1 + R_2S_2 \rightarrow R_1S_1{\cdot}R_2 + R_1S_1{\cdot}S_2$ **or** $R_2S_2{\cdot}R_1 + R_2S_2{\cdot}S_1$ **(Eq. 4)**

Scheme 2. Potential outcomes of the cocrystallization trials between racemic compounds.

Etiracetam, mandelic acid and proline were chosen as reference compounds, as numerous examples of cocrystallization involving these compounds are described in the literature. [30-32] Furthermore, the formation of conglomerates of all three compounds by cocrystallization with achiral coformers has been reported.[26, 29, 33] Finally, in our earlier work we reported a stable conglomerate between the two racemic compounds RS-etiracetam and RS-mandelic acid according to equation 3.[28]

Table 1 shows the screening to reveal the existence of 16 cocrystal phases, 3 of which have been reported previously.[28, 34, 35] As mentioned above, the experimental XRPD patterns from the grinding experiments were found identical to those simulated using the single crystal data (fig. ESI-12-26).

Besides the formation of new cocrystals, 3 previously unreported polymorphs of the starting materials were discovered (Fig. ESI-9-11). Moreover, while the polymorphs of RS-3-chloromandelic acid and DL-proline hydrate were racemic compounds, in one of the recrystallization trials involving DL-3-phenyllactic acid and DL-proline cocrystal, the crystallization of a new polymorphic conglomerate of D-/L-3-phenyllactic acid was observed.

Table 1. Cocrystallization outcomes analysed by XRPD. ✓ - cocrystal; ✓* - published cocrystal; ✗- physical mixture of racemates. Uppercase numbering corresponds to the reaction outcome.

	Etiracetam	Mandelic acid	Proline
2-phenylbutyric acid	✗	✗	✓ (1)
3-phenyllactic acid	✗	✗	✓ (1)
Ibuprofen	✗	✗	✓ (1)
Methylsuccinic acid	✗	✗	✓ (1)
Tartaric acid	✗	✗	✗
Flurbiprofen	✓ (1)	✗	✓* (1)
Naproxen	✗	✗	✓* (1)
Phenylsuccinic acid	✗	✗	✓ (1)
Tropic acid	✗	✗	✓ (1)
2-chloromandelic acid	✓* (3)	✗	✗
3-chloromandelic acid	✓ (1)	✗	✓ (1)
2-fluoromandelic acid	✓ (3)	✗	✓ (1)
Proline	✗	✓ (1)	
Mandelic acid	✓* (3)		

Etiracetam

Cocrystal formation with RS-etiracetam and RS-mandelic acid shows the typical relatively low success rate expected for cocrystallization trials. RS-etiracetam cocrystallizes with RS-flurbiprofen and RS-3-chloromandelic acid, according to equation 1, in a full racemic crystal form containing both enantiomers of both compounds. As mentioned above, the cocrystallization of RS-mandelic acid with RS-etiracetam resulted in the formation of conglomerates.[28]

Surprisingly, DL-Proline seems to be a very potent cocrystal former, with 11 cocrystal systems identified using this compound. Only DL-tartaric acid and RS-2-chloromandelic acid failed to cocrystallize with DL-proline. Furthermore, all of the obtained cocrystals were found to be anhydrous which is unusual for proline cocrystals, for which numerous cocrystal hydrate phases have been reported previously.[34, 35] All cocrystals react according to equation 1, being full racemic compounds.

All cocrystals found in this work form in a 1 to 1 stoichiometric ratio, with exception of the cocrystal involving flurbiprofen and etiracetam which forms a 2 to 1 cocrystal. As shown in table 1, none of the combinations resulted in the outcome of equation 4 (conglomerate involving a racemate of 1 compound and an enantiopure version of the second compound). 14 cocrystals were found to be full racemic compounds (Scheme 2, Eq. 1). Three conglomerates (eq. 3) were formed all involving etiracetam and one of the mandelic acid coformers, mandelic acid, 2-fluoro- or 2-chloromandelic acid. Rather surprisingly, all three cocrystal structures were found isostructural (Fig. 1) a result that was unexpected, especially for the 2-chloro derivative, given its much larger size.[28] According to Table 1, conglomerate formation by a combination of two racemic compounds is a rather rare phenomenon.

To avoid a simple enumeration of the crystal structures of the obtained cocrystals, only the most interesting ones from the authors' point of view will be discussed in this manuscript while all the remaining will be shown in the supporting information (Fig. ESI-1-8).

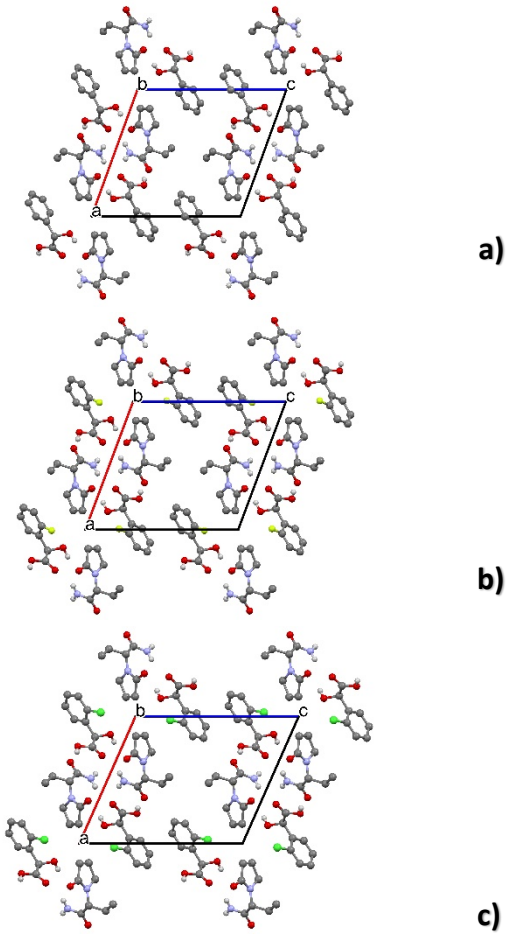

Fig. 1. Unit cells of the conglomerate cocrystals of MA·ETI (refcode YASGIK,[36] **a**), 2-FMA·ETI **b**) and 2-ClMA·ETI (refcode QEFCIR,[37] **c**). View along crystallographic b-axis; H_{CH} atoms are omitted for clarity.

Even though three conglomerates appear when combining two racemic compounds, they are isomorphous. The formation of an isomorphous cocrystal of 2-fluoromandelic acid with etiracetam to the one with the unsubstituted mandelic acid and etiracetam can be explained by the relatively small difference in size between fluorine and hydrogen atoms (Kitaigorodskii's coefficient for geometrical similarity[38]) with several examples of F/H solid solutions reported in the literature. [39, 40] At the same time, the isomorphous cocrystal with 2-chloromandelic acid was more difficult to foresee. Indeed, the cocrystallization of etiracetam with 3-chloromandelic acid led to the formation of a racemic cocrystal with different hydrogen bonding interactions (Fig. 2). The cocrystal of S-2-chloromandelic acid-Levetiracetam has recently been used in the context of an enantiospecific resolution.[37]

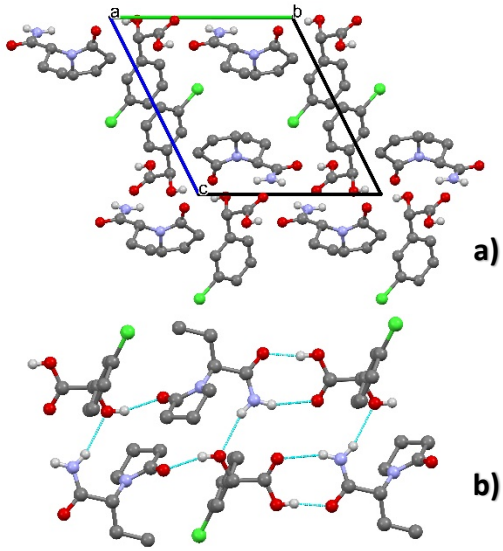

Fig. 2. Unit cell (a) viewed along the crystallographic a-axis and (b) hydrogen bonding interactions in the etiracetam with 3-chloromandelic acid cocrystal. HCH atoms are omitted for clarity. H_{CH} atoms are omitted for clarity.

All other combinations led to the formation of full racemic compounds (both enantiomers of both compounds present). The cocrystal between flurbiprofen with etiracetam led to the formation of a cocrystal that might be considered a co-drug. Enantiopure S-etiracetam (levetiracetam, sold under the brand name Keppra) is a drug used to treat epilepsy.[41] Flurbiprofen, a nonsteroidal anti-inflammatory drug, has also been reported to lower the convulsive threshold.[42] As has already been mentioned above, this cocrystal is the only one described in this manuscript that has a stoichiometric ratio different from 1:1, with two molecules of flurbiprofen and one of etiracetam in the asymmetric unit (Fig. 3). One flurbiprofen molecule interacts with etiracetam via a carboxylic acid through an amide $R^2_2(8)$ HB synthon, while the other interacts via an $R^2_2(11)$ HB synthon formed by the carboxyl group and H_{NH} from the amide group and $O_{C=O}$.

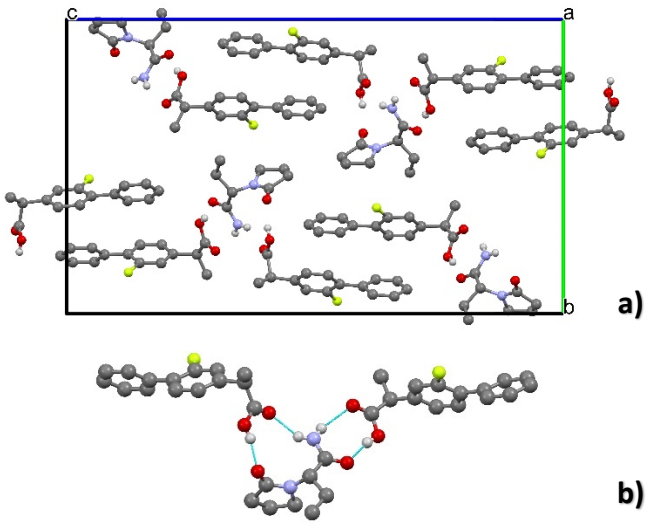

Fig. 3. $(FLU)_2$·ETI. Crystal packing (a) and hydrogen bonding interactions (b); H_{CH} atoms are omitted for clarity.

Another interesting observation during this work occurred during attempts to obtain single crystals of 2-FMA·PRO, as a polymorphic system of this cocrystal was identified. The first polymorph, which was found to match the one obtained mechanochemically (see ESI-14), crystallizes in the triclinic crystal system with one molecule of each reagent in the asymmetric unit. This form is a true cocrystal with proline being in zwitterionic form and 2-fluoromandelic acid being protonated (Fig. 4).

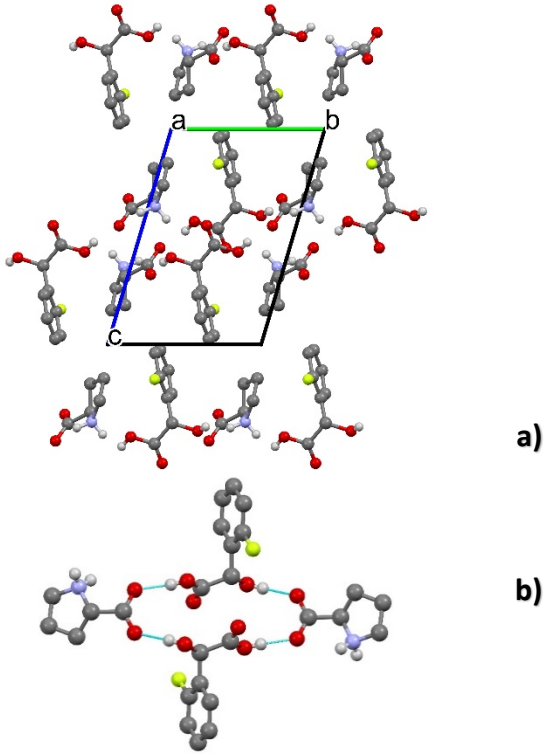

Fig. 4. Crystal packing **(a)** and hydrogen bonding interactions **(b)** in 2-FMA·PRO form I. H_{CH} atoms are omitted for clarity.

In the second form, in turn, the carboxyl groups of both acids are partially protonated – with the proton being equally distributed between both of them (Fig. 5) based upon analysis of the electron density map. Consequently, 2-FMA·PRO can be considered to be somewhere between a salt and a cocrystal. It crystallizes in the monoclinic crystal system with one molecule of both coformers in the asymmetric unit. This system nicely highlights the so-called- salt-cocrystal continuum,[43] with only very little structural difference needed to go from a cocrystal to a salt. It should be noted that in all other cocrystals, proline is in zwitterionic form leading therefore to true cocrystals.

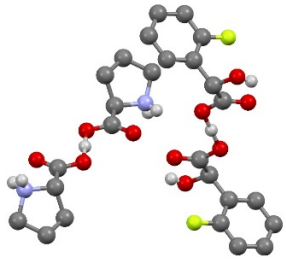

Fig. 5. Partial protonation of both acids in 2-FMA·PRO form II. H_{CH} atoms are omitted for clarity.

Conclusions

In this contribution, we investigated the likelihood of forming a conglomerate when combining two racemic compounds. Based on the performed screening, we conclude this likelihood to be low, with a clear preference for a racemic compound of the type R_1S_1·R_2S_2 over the conglomerate. Even though 3 conglomerates were identified, they all belong to the etiracetam-mandelic acid derivative family. These results show the simultaneous preferential cocrystallization process developed in our previous research to be limited to specific cases.[28] Meanwhile, the role of proline in crystal engineering is again emphasized. This compound is clearly an excellent cocrystal former.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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