Staurosporine

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**General Information**

- CAS-Number: 62996-74-1
- Chemical formula: C_{28}H_{26}N_{4}O_{3}
- Molecular weight: 466.5 g/mol
- Melting point: 237-239°C
- IUPAC: (9S,10R,11R,13R)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-11-(methylamino)-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:2',1'-Im]pyrrolo[3,4-j] [1,7]benzodiazonin-1-one
- Soluble in DMSO, methanol, ethanol (not in Water)
- Appearance: crème-colored to light yellow powder
- Costs: 100mg => 855€

**Origin**

Staurosporine is an originally marine alkloid isolated from Streptomyces Staurosporeus in 1977. Streptomyces is an actinobacteria from which many antibiotics were isolated before. They are mostly gramm-positive and they have a specific mycel-forming structure.

In 1994 the structure was clarified by use of X-Ray analysis. The structure resembles the structure of ATP (Adenosine Triphosphate) and because of that fits perfectly to the binding regions of ATP-dependent protein kinases.

Consequently it was figured that it inhibits only one kind of protein kinases but this was later refuted seeing that Staurosporine inhibits amongst others Calcium/Calmodulin-dependent Kinases and EGF-R. It was declared as a broad-spectrum Kinase inhibitor.
Staurosporine is shown as green, blue and red circles and the protein kinase is shown in yellow and purple.

**Biosynthesis**

The biosynthesis starts with the L-amino acid thryptophan and is catalyzed by enzymes.

**Kinases generally and their interaction with Staurosporine**

In general kinases catalyze the transfer of ATP’s phosphate group to other molecules. The human body has more than 500 different kinases which are responsible for control and signal transduction and they influence metabolism, cell growth, differentiation and apoptosis.

Particularly the kinases responsible in the cell cycle control, called CDKs (cyclin dependent Kinases) are important when it is talked about the effect of Staurosporine.
The structural resemblance from ATP and Staurosporine led to the question which molecule is better compatible to the kinase binding regions. Staurosporine is higher affine but less selective to a specific kinases. This is the reason why in comparison with ATP, Staurosporine bind stronger to the kinase and the removal is more difficult.

Moreover ATP is able to rotate a lot more bonds then Staurosporine caused by the chemical indol and aromatic ring structure. This causes a fixation of some Kinase amino acids and a structural adaption or a conformational selection.

**Effect of Staurosporine**

Formerly Staurosporine should be used as a medication for cancer and as an antibiotic. But it was detected that it is much too toxic to use it as a therapeutic approach. It begins to operate in small concentrations which can be deduced because of the high affinity to kinases.

As an antibiotic it operates as an inducer for apoptosis. Apoptosis is the controlled way of cell death and the consequence is the dialysis of the cell. This process is irreversible. Staurosporine can influence the apoptosis in 2 different ways, the first is the fast, caspase dependent way and the second way the slower caspase independent way. And if Staurosporine binds to CDK2 and CDK5 in the cell cycle the important checkpoints cannot be passed and the cell is forced to go to apoptosis instead of differentiating.
Derivates of Staurosporine

Due to the high toxicity of Staurosporine the academics search for derivates with better characteristics in cancer therapy. Therefore it is important that the molecules get more specific for certain kinases. CGP 41251, UCN-01 and Bryostatin were discovered and have been in clinical studies since 1998.

The effect of CGP 41251 is that it operates as an Inhibitory in lung cancer medication. It also effects the growth of brain cancer. UCN-01 is as well inserted in brain cancer therapy and in relation with leukemia and breast cancer.

In contrast Bryostatin is an activator and stimulates the own immune system.
Sources:

- http://www.fermentek.co.il/staurosporin.htm (zuletzt besucht am 26.06.2013)
- http://freespace.virgin.net/clive.walker1/staurosporine/staurosporine2.html (zuletzt besucht am 26.06.2013)
- „Staurosporine induces apoptosis through both caspase-dependent and caspase-independent mechanisms”; Belmokthar; 2001; Nature Publishing Group
- “Aktivierung eines neuartigen Apoptose-Signalweges durch den Proteinkinaseinhibitor Staurosporin”; Dobrawa; 2009; Institut für Biologische Chemie und Ernährungswissenschaft Universität Hohenheim

->Images:

- Image 1: http://www.scharfphoto.com/fine_art_prints/archives/199901-008-Streptomycyes.jpg
- Image 2: http://www.beilstein-institut.de/Bozen2008/Proceedings/Meggers/images/Bozen2008_07_02.jpg
- Image 4: http://freespace.virgin.net/clive.walker1/staurosporine/1stc_show.gif
- Image 5: http://origin-ars.els-cdn.com/content/image/1-s2.0-S030636239800069X-gr2b.gif