

Supporting Information:

Discovery of a novel IKK- β inhibitor by ligand-based virtual screening techniques

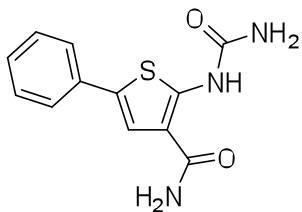
Stefan M. Noha, Atanas G. Atanasov, Daniela Schuster, Patrick Markt, Nanang Fakhrudin, Elke H. Heiss, Olivia Schrammel, Judith M. Rollinger, Hermann Stuppner, Verena M. Dirsch, and Gerhard Wolber

This supporting material document contains

- 1) All compounds from the literature dataset as referenced in the manuscript including references to all the articles introducing the compounds.
- 2) A detailed experimental description of the parameters for the docking study.

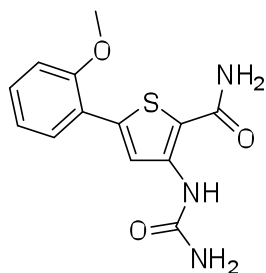
1) IKK- β Literature-Dataset

Baxter et al., 2004¹

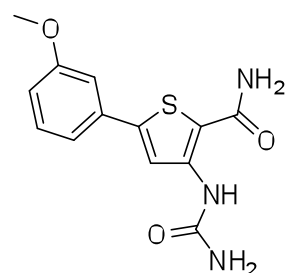


CAS 354811-10-2
 $IC_{50} = 13 \text{ nM}$

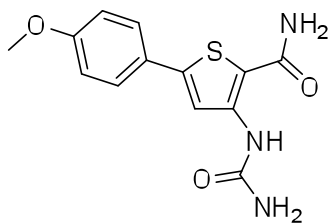
compound 4



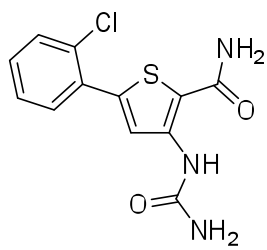
CAS 354811-06-6
 $IC_{50} = 200 \text{ nM}$



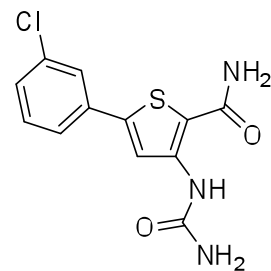
CAS 354811-09-9
 $IC_{50} = 300 \text{ nM}$



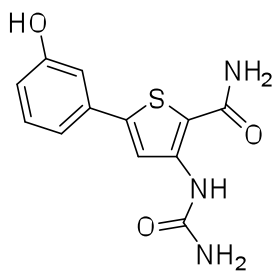
CAS 354810-95-0
 $IC_{50} = 50 \text{ nM}$



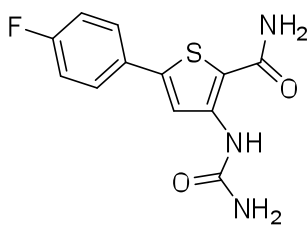
CAS 354811-04-4
 $IC_{50} = 100 \text{ nM}$



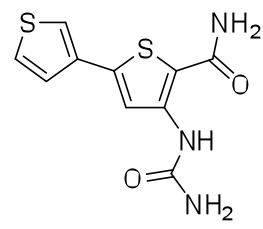
CAS 354810-83-6
 $IC_{50} = 40 \text{ nM}$



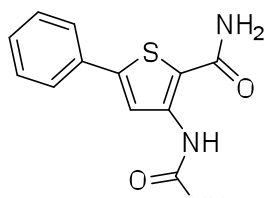
CAS 354811-01-1
 $IC_{50} = 100 \text{ nM}$



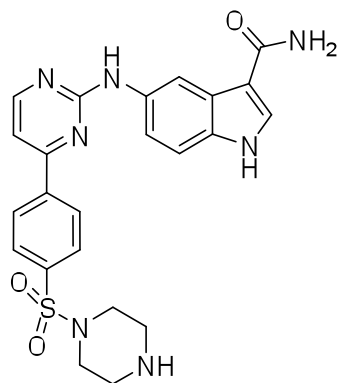
CAS 354810-86-9
 $IC_{50} = 63 \text{ nM}$



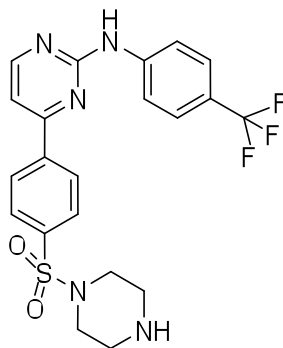
CAS 354810-98-3
 $IC_{50} = 63 \text{ nM}$



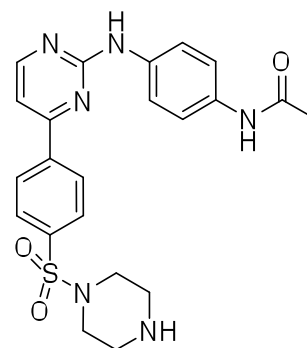
CAS 354810-80-3
 $IC_{50} = 25 \text{ nM}$



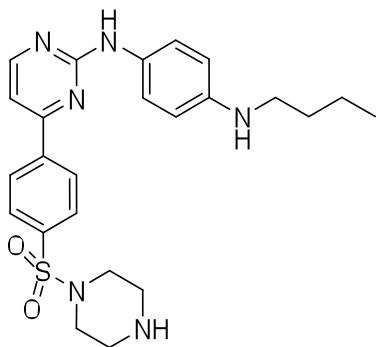
CAS 677753-06-9
IC₅₀ = 550 nM



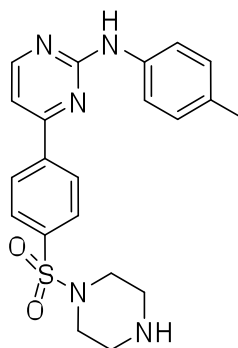
CAS 677753-07-0
IC₅₀ = 513 nM



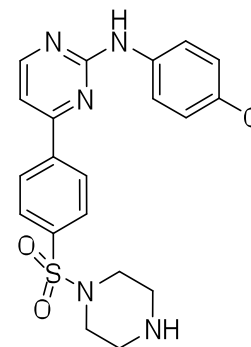
CAS 677753-08-1
IC₅₀ = 331 nM



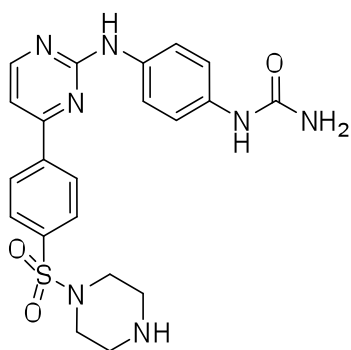
CAS 677753-09-2
IC₅₀ = 309 nM



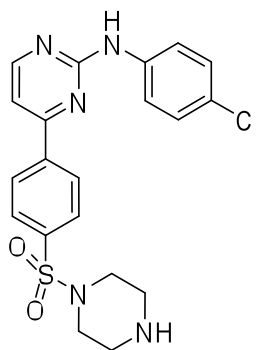
CAS 677753-10-5
IC₅₀ = 269 nM



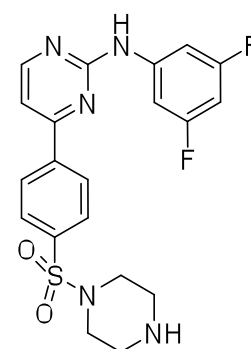
CAS 677753-11-6
IC₅₀ = 214 nM



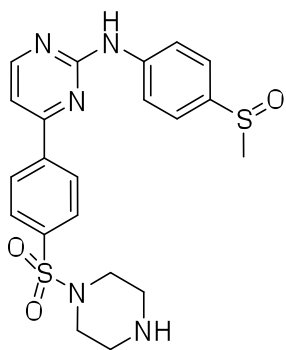
CAS 677753-12-7
IC₅₀ = 155 nM



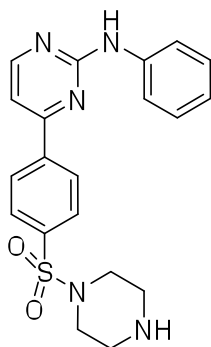
CAS 677753-13-8
IC₅₀ = 148 nM



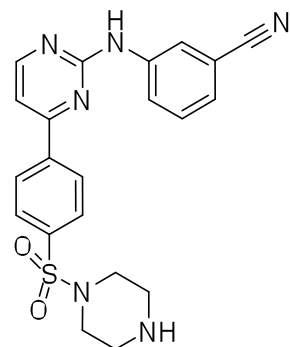
CAS 677753-14-9
IC₅₀ = 117 nM



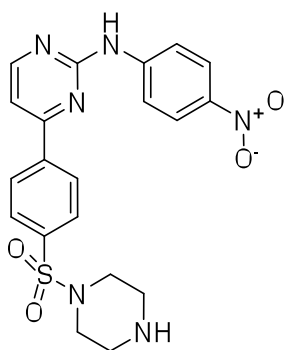
CAS 677753-15-0
IC₅₀ = 91 nM



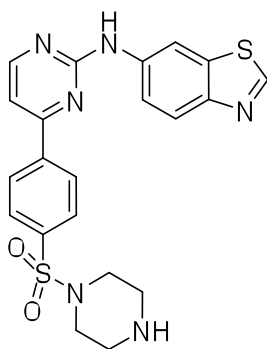
CAS 677753-16-1
IC₅₀ = 91 nM



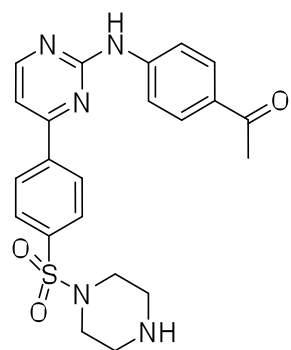
CAS 677753-17-2
IC₅₀ = 83 nM



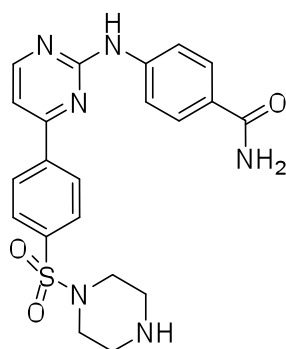
CAS 677753-18-3
IC₅₀ = 66 nM



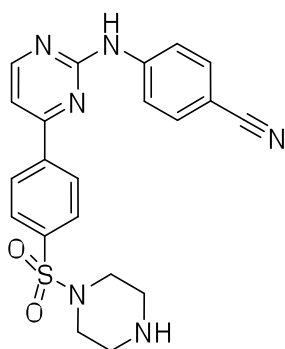
CAS 677753-19-4
IC₅₀ = 60 nM



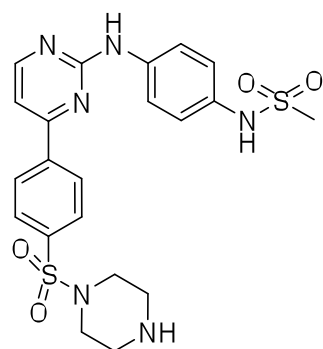
CAS 677753-20-7
IC₅₀ = 59 nM



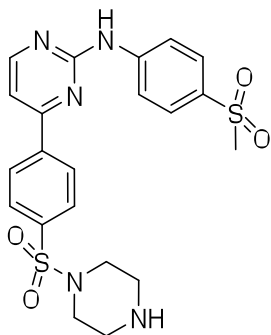
CAS 677753-20-8
IC₅₀ = 48 nM



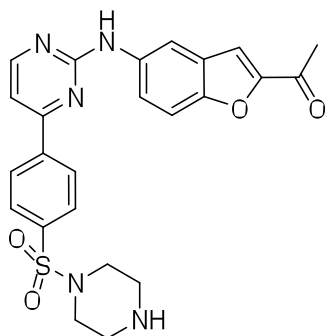
CAS 677753-22-9
IC₅₀ = 44 nM



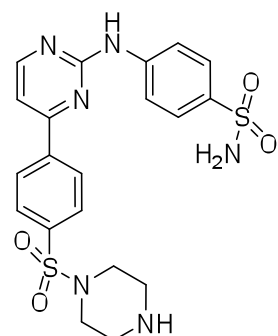
CAS 677753-23-0
IC₅₀ = 43 nM



CAS 677753-24-1
IC₅₀ = 31 nM

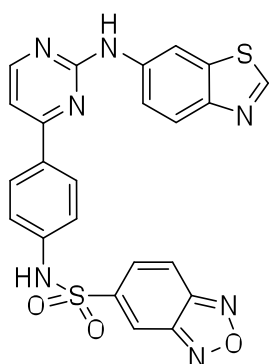


CAS 677753-25-2
IC₅₀ = 26 nM

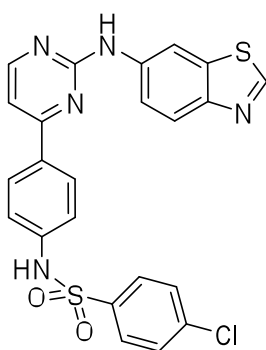


CAS 677753-26-3
IC₅₀ = 11 nM
compound 5

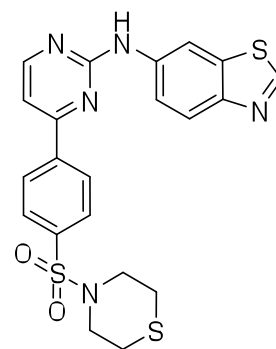
Bingham et al., 2008³



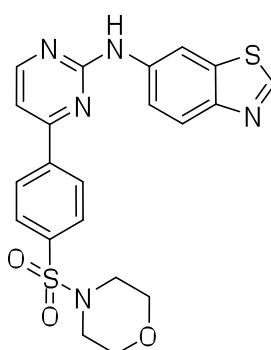
CAS 1042947-36-3
IC₅₀ = 230 nM



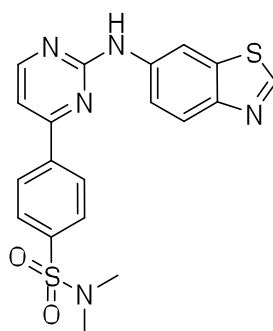
CAS 1042947-38-3
IC₅₀ = 990 nM



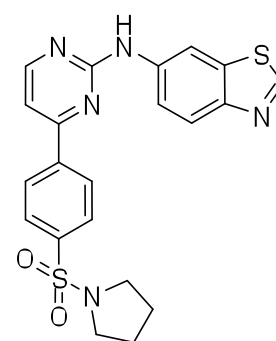
CAS 1042947-48-7
IC₅₀ = 250 nM



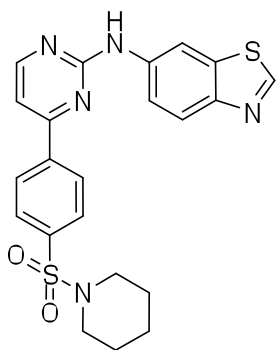
CAS 1042947-50-1
IC₅₀ = 380 nM



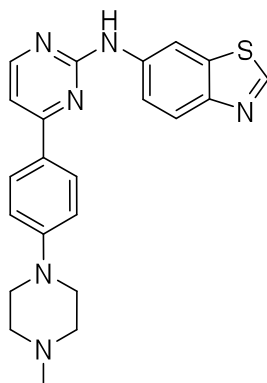
CAS 1042947-53-4
IC₅₀ = 410 nM



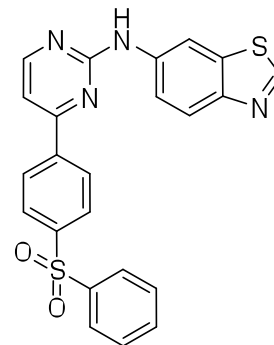
CAS 1042947-55-6
IC₅₀ = 540 nM



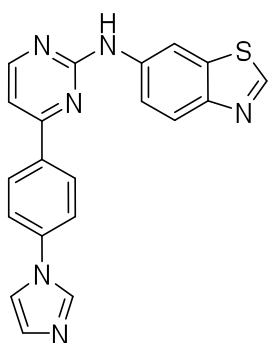
CAS 1042947-58-9
 $IC_{50} = 600 \text{ nM}$



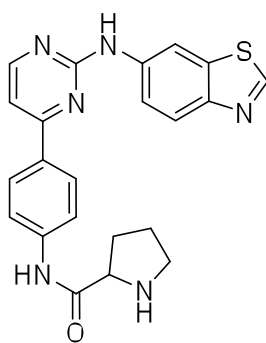
CAS 1042947-07-8
 $IC_{50} = 410 \text{ nM}$



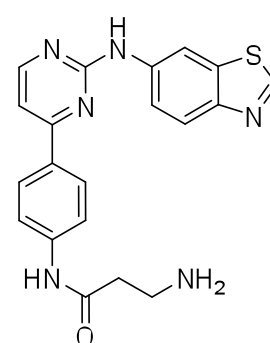
CAS 1042947-08-9
 $IC_{50} = 440 \text{ nM}$



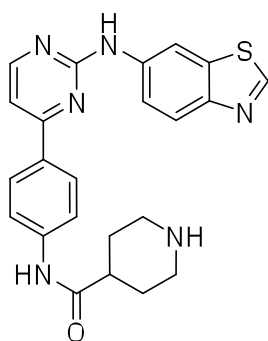
CAS 1042947-10-3
 $IC_{50} = 700 \text{ nM}$



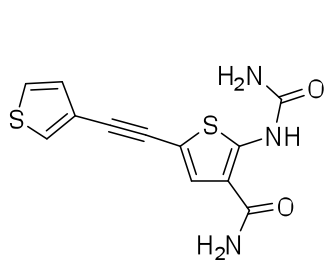
CAS 1042947-29-4
 $IC_{50} = 130 \text{ nM}$



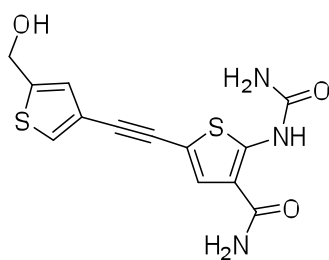
CAS 1042947-31-8
 $IC_{50} = 270 \text{ nM}$



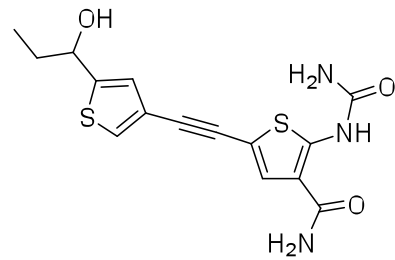
CAS 1042947-34-1
 $IC_{50} = 400 \text{ nM}$



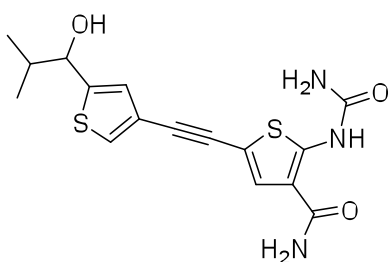
CAS 859809-23-7
IC₅₀ = 420 nM



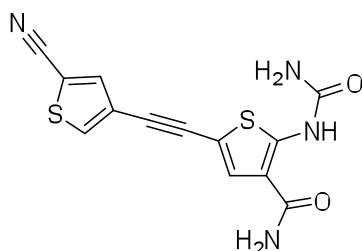
CAS 859809-24-8
IC₅₀ = 195 nM



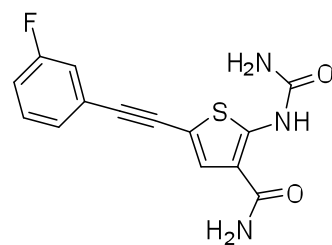
CAS 859809-25-9
IC₅₀ = 465 nM



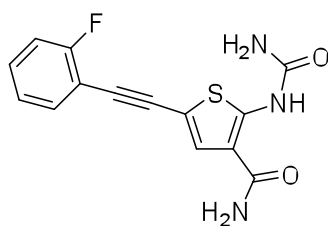
CAS 859809-26-0
IC₅₀ = 563 nM



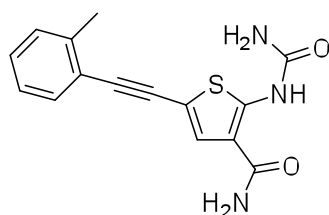
CAS 859809-27-1
IC₅₀ = 333 nM



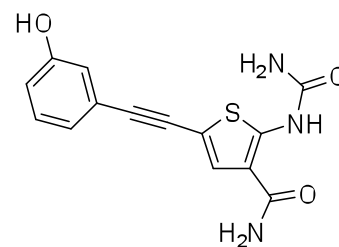
CAS 859809-28-2
IC₅₀ = 331 nM



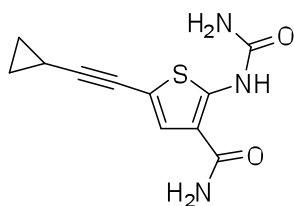
CAS 859809-29-3
IC₅₀ = 620 nM



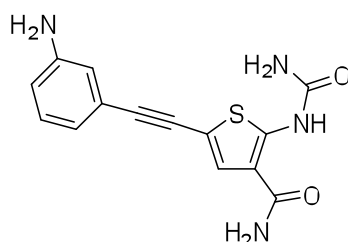
CAS 859809-31-7
IC₅₀ = 716 nM



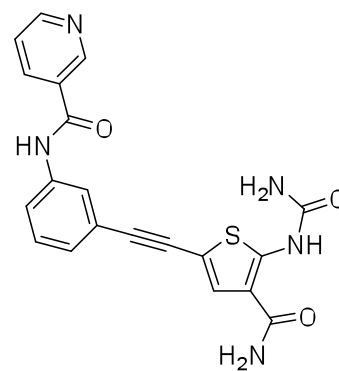
CAS 859809-32-8
IC₅₀ = 303 nM



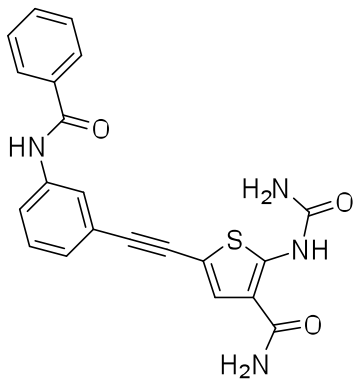
CAS 859809-33-9
IC₅₀ = 273 nM



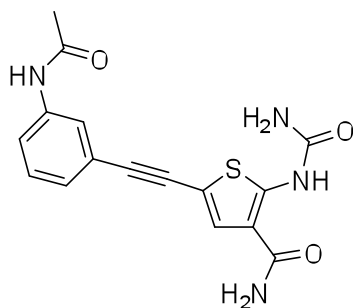
CAS 859809-34-0
IC₅₀ = 709 nM



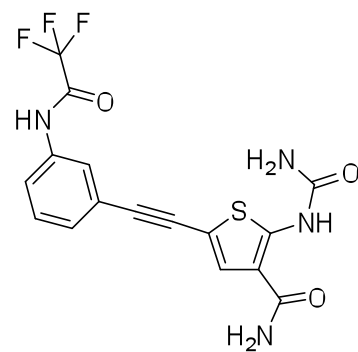
CAS 859809-36-2
IC₅₀ = 557 nM



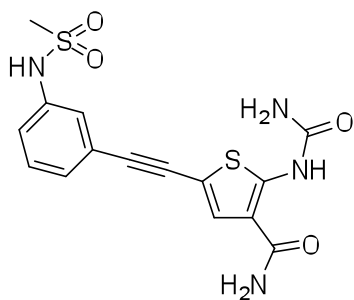
CAS 859809-38-4
 $IC_{50} = 704 \text{ nM}$



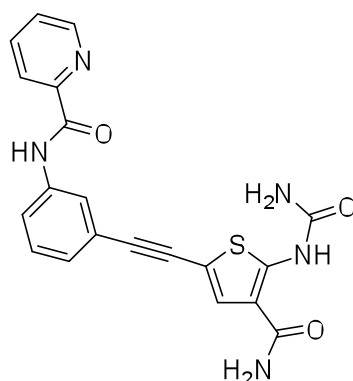
CAS 859809-39-5
 $IC_{50} = 964 \text{ nM}$



CAS 859809-40-8
 $IC_{50} = 980 \text{ nM}$

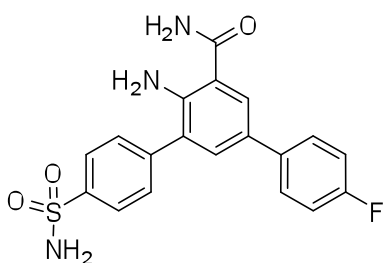


CAS 859809-43-1
 $IC_{50} = 454 \text{ nM}$

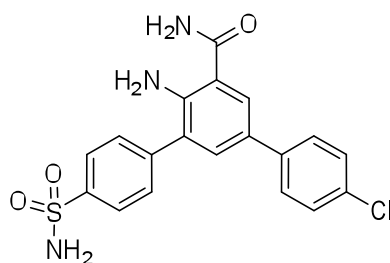


CAS 859809-35-1
 $IC_{50} > 20 \text{ }\mu\text{M}$

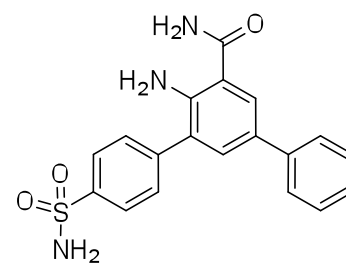
Christopher et al., 2007⁵



928655-85-0
 $IC_{50} = 200 \text{ nM}$

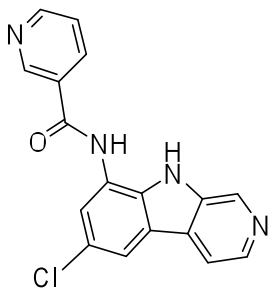


928655-63-4
 $IC_{50} = 100 \text{ nM}$

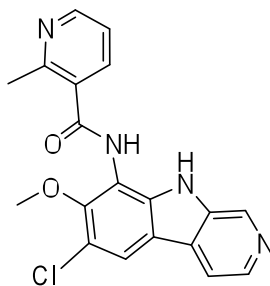


928655-16-0
 $IC_{50} = 251 \text{ nM}$

Newton et al., 2007⁶

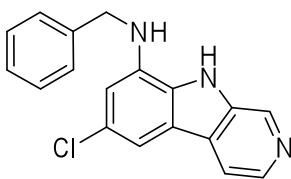


PS-1145
CAS 431898-65-6
IC₅₀ = 150 nM

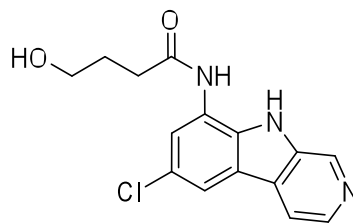


ML 120B
CAS 783348-36-7
IC₅₀ = 60 nM

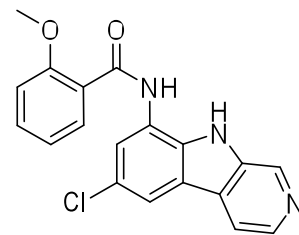
Castro et al., 2003⁷



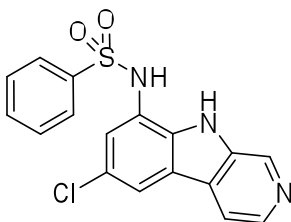
CAS 590398-78-0
IC₅₀ > 20 μM



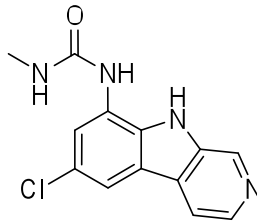
CAS 590398-81-5
IC₅₀ > 20 μM



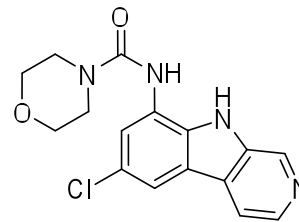
CAS 590398-88-2
IC₅₀ > 20 μM



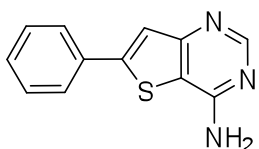
CAS 590398-93-9
IC₅₀ > 20 μM



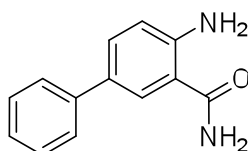
CAS 590398-96-2
IC₅₀ > 20 μM



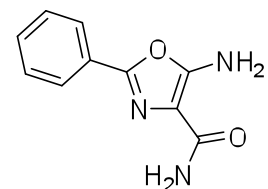
CAS 590398-98-4
IC₅₀ > 20 μM



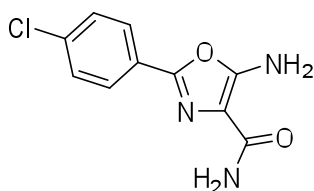
CAS 663918-11-4
 $IC_{50} = 970 \text{ nM}$



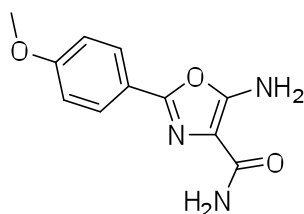
CAS 890402-92-3
 $IC_{50} = 14.5 \text{ }\mu\text{M}$



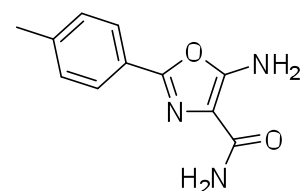
CAS 99185-68-9
 $IC_{50} = 11 \text{ }\mu\text{M}$



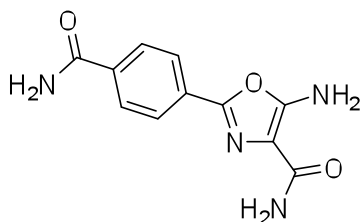
CAS 890402-94-5
 $IC_{50} = 13.6 \text{ }\mu\text{M}$



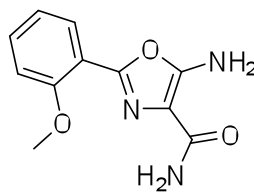
CAS 890402-95-6
 $IC_{50} = 17.7 \text{ }\mu\text{M}$



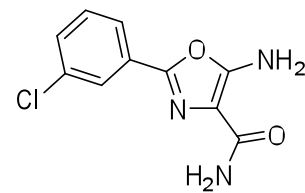
CAS 890402-96-7
 $IC_{50} = 12.7 \text{ }\mu\text{M}$



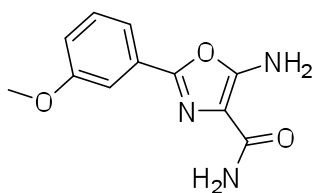
CAS 890402-98-9
 $IC_{50} = 25.8 \text{ }\mu\text{M}$



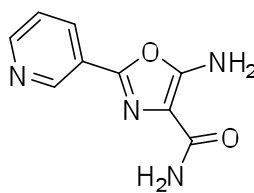
CAS 890403-00-6
 $IC_{50} = 36.2 \text{ }\mu\text{M}$



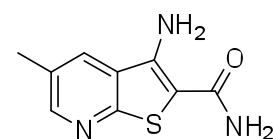
CAS 890403-02-8
 $IC_{50} = 10.6 \text{ }\mu\text{M}$



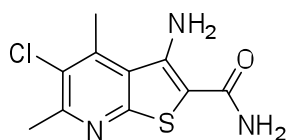
CAS 890403-03-9
 $IC_{50} = 13.9 \text{ }\mu\text{M}$



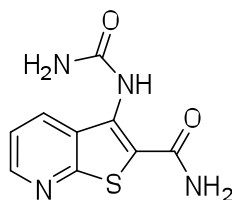
CAS 890403-07-3
 $IC_{50} = 35.7 \text{ }\mu\text{M}$



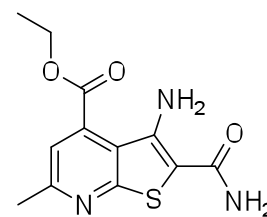
CAS 890403-08-4
 $IC_{50} = 19.9 \text{ }\mu\text{M}$



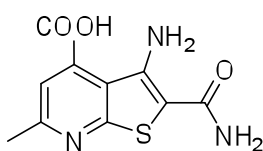
CAS 849425-30-5
 $IC_{50} > 27.5 \mu M$



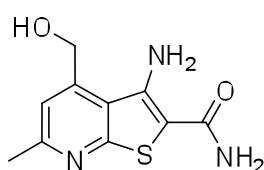
CAS 890403-09-5
 $IC_{50} > 50 \mu M$



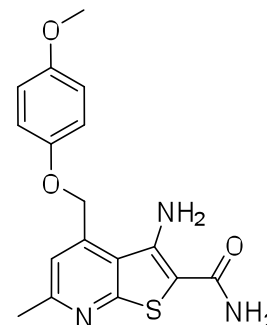
CAS 635731-83-8
 $IC_{50} = 15.1 \mu M$



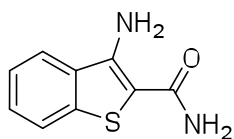
CAS 635731-85-0
 $IC_{50} > 49 \mu M$



CAS 635731-89-4
 $IC_{50} = 12.7 \mu M$

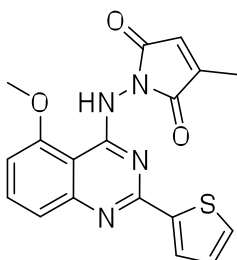


CAS 890403-11-9
 $IC_{50} = 13 \mu M$

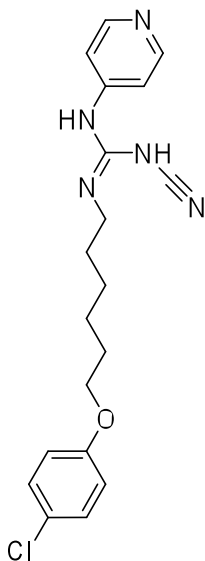


CAS 37839-59-1
 $IC_{50} = 12.6 \mu M$

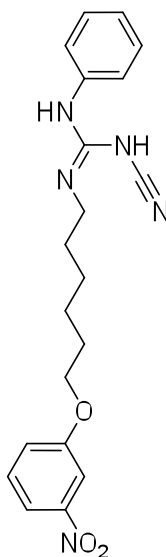
Palanki et al., 2003⁹



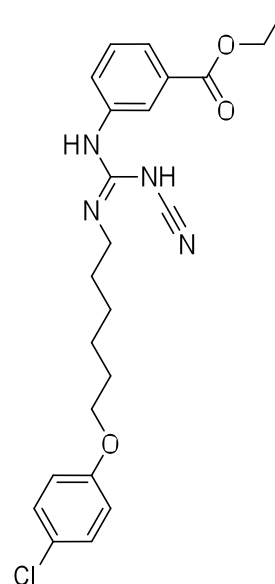
SPC 839
CAS 219773-55-4
 $IC_{50} = 62 nM$



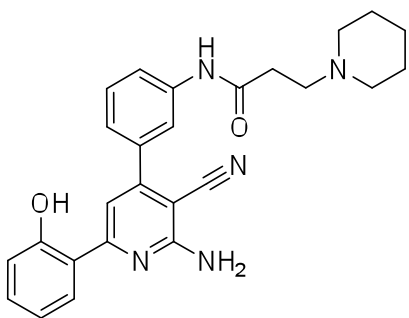
CHS-828
CAS 200484-11-3
 $IC_{50} = 8 \text{ nM}$



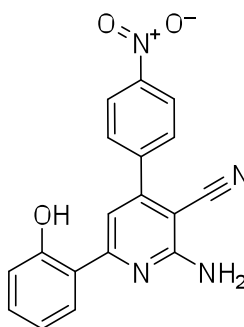
EO 759
CAS 476156-99-7
 $IC_{50} > 10 \text{ }\mu\text{M}$



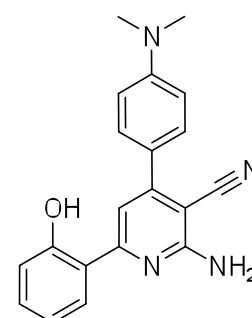
EO 807
CAS 476157-00-3
 $IC_{50} > 10 \text{ }\mu\text{M}$



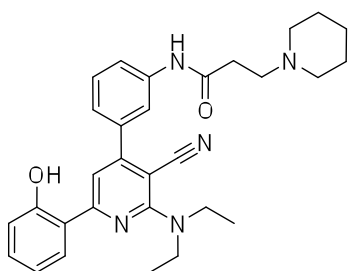
CAS 433957-88-1
 $IC_{50} = 600 \text{ nM}$



CAS 224818-33-1
 $IC_{50} > 20 \text{ }\mu\text{M}$

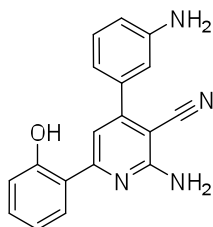


CAS 224818-37-5
 $IC_{50} > 20 \text{ }\mu\text{M}$

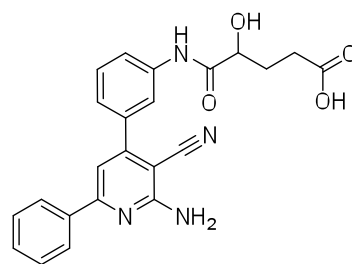


CAS 553635-45-3
IC₅₀ = 20 μM

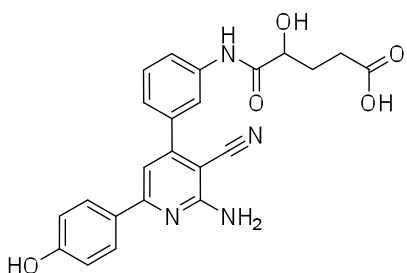
compound 7



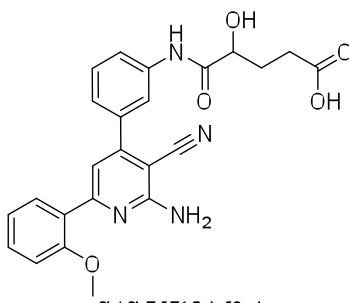
CAS 433958-64-6
IC₅₀ = 20 μM



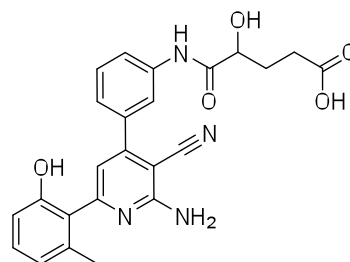
CAS 553635-52-2
IC₅₀ > 20 μM



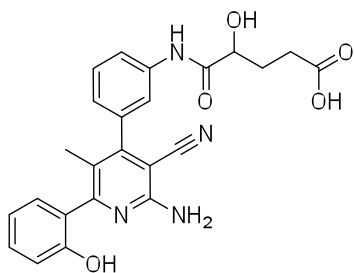
CAS 553635-53-3
IC₅₀ > 20 μM



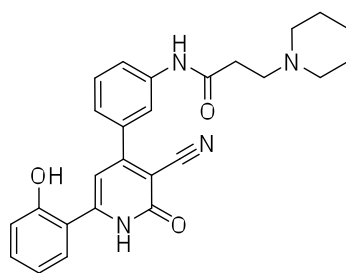
CAS 757184-52-4
IC₅₀ > 20 μM



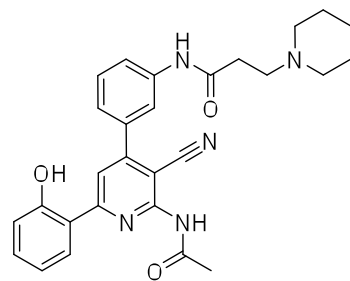
CAS 780035-19-0
IC₅₀ > 20 μM



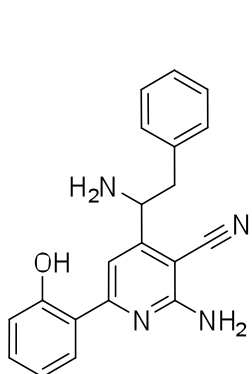
CAS 771472-73-2
IC₅₀ > 20 μM



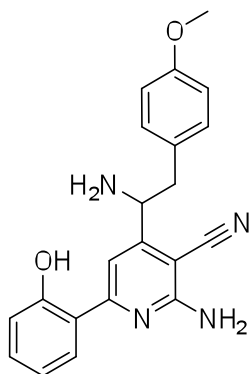
CAS 789487-07-6
IC₅₀ > 20 μM



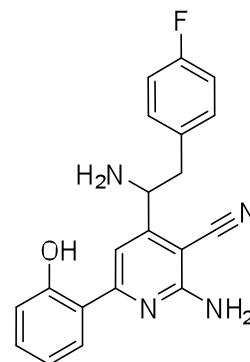
CAS 433958-95-3
IC₅₀ = 15 μM



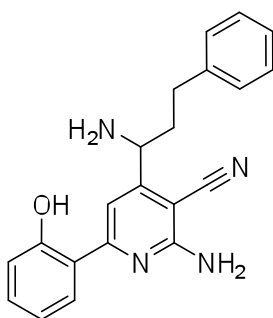
CAS 763083-78-9
IC₅₀ = 60 nM



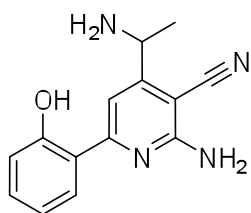
CAS 744215-79-0
IC₅₀ = 80 nM



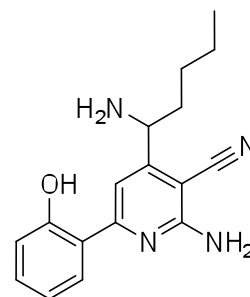
CAS 744215-80-3
IC₅₀ = 40 nM



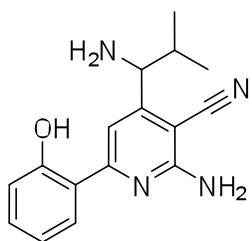
CAS 744215-81-4
IC₅₀ = 730 nM



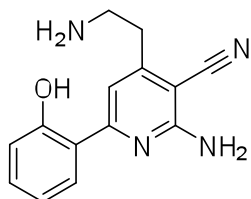
CAS 744215-82-5
IC₅₀ = 150 nM



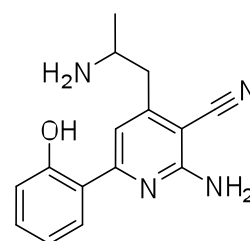
CAS 744215-83-6
IC₅₀ = 480 nM



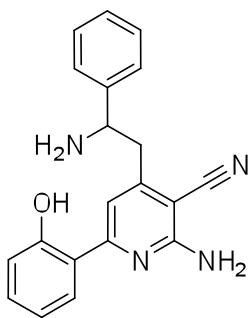
CAS 763083-78-9
IC₅₀ = 60 nM



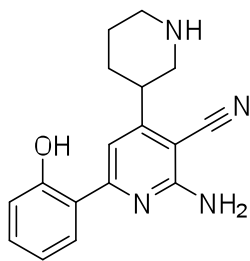
CAS 406209-10-7
IC₅₀ = 70 nM



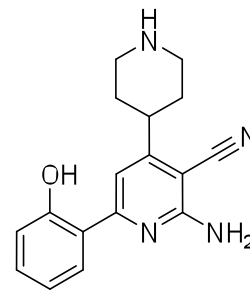
CAS 406209-08-3
IC₅₀ = 470 nM



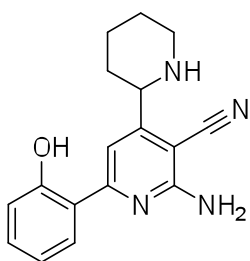
CAS 744215-85-8
 $IC_{50} = 110 \text{ nM}$



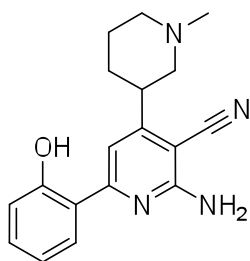
CAS 744215-99-4
 $IC_{50} = 25 \text{ nM}$



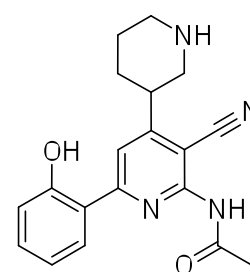
CAS 406208-79-5
 $IC_{50} = 300 \text{ nM}$



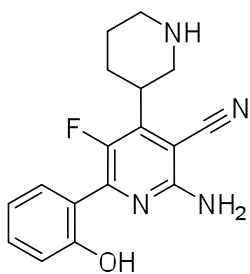
CAS 744216-02-2
 $IC_{50} = 530 \text{ nM}$



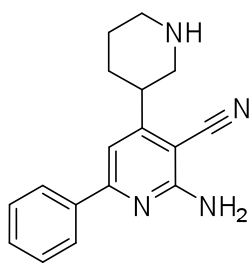
CAS 744216-03-3
 $IC_{50} = 230 \text{ nM}$



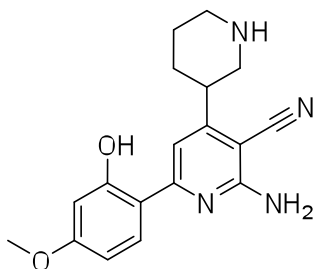
CAS 737749-44-9
 $IC_{50} = 330 \text{ nM}$



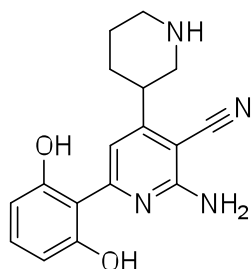
CAS 406208-69-3
 $IC_{50} = 230 \text{ nM}$



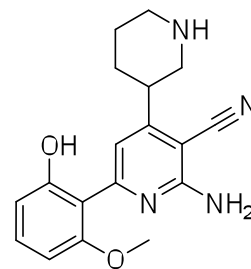
CAS 744216-04-4
 $IC_{50} > 20 \text{ }\mu\text{M}$



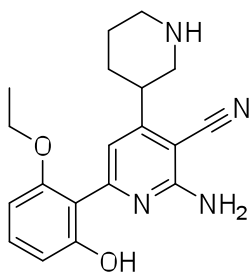
CAS 744217-81-0
IC₅₀ = 560 nM



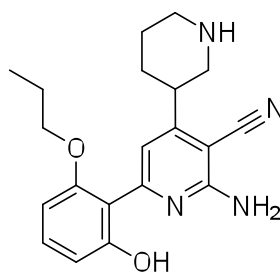
CAS 744910-98-2
IC₅₀ = 15 nM



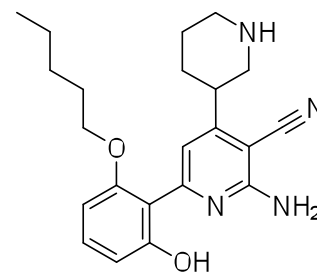
CAS 721394-10-1
IC₅₀ = 34 nM



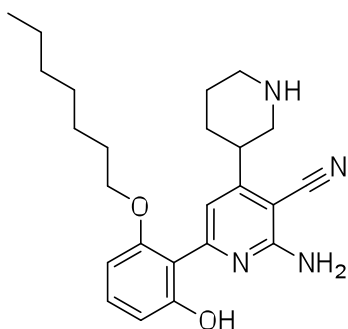
CAS 744217-83-2
IC₅₀ = 14 nM



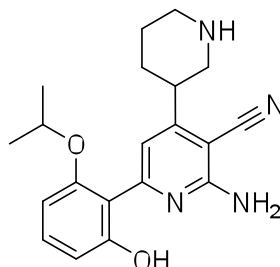
CAS 406208-17-1
IC₅₀ = 5 nM



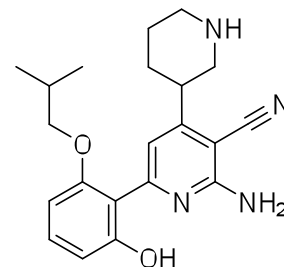
CAS 744217-84-3
IC₅₀ = 6 nM



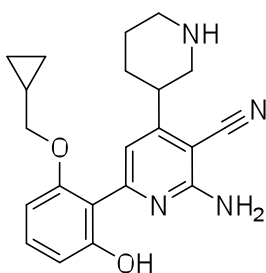
CAS 744217-85-4
IC₅₀ = 14 nM



CAS 744217-86-5
IC₅₀ = 81 nM



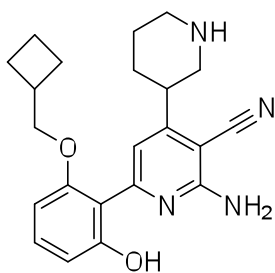
CAS 744217-87-6
IC₅₀ = 5 nM



CAS 732239-51-9

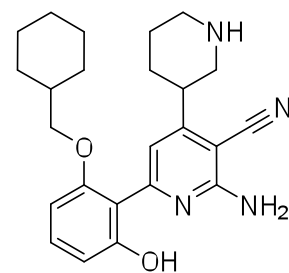
IC₅₀ = 3 nM

compound 3



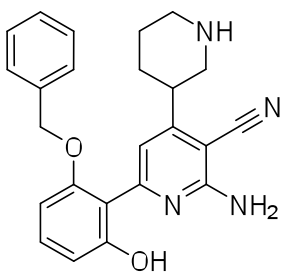
CAS 406208-21-7

IC₅₀ = 4 nM



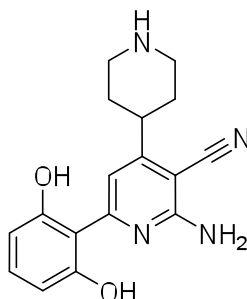
CAS 744217-88-7

IC₅₀ = 26 nM



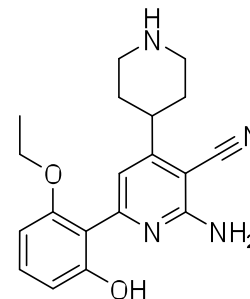
CAS 406208-16-0

IC₅₀ = 9 nM



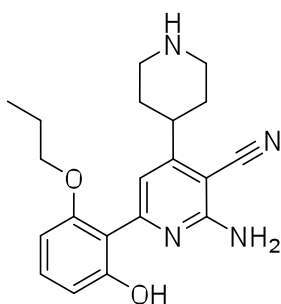
CAS 744217-98-8

IC₅₀ = 270 nM



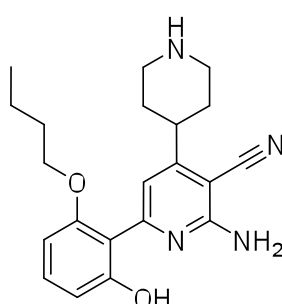
CAS 744217-90-1

IC₅₀ = 120 nM



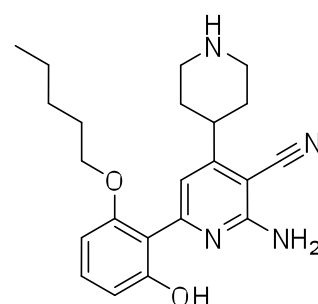
CAS 406208-52-4

IC₅₀ = 24 nM



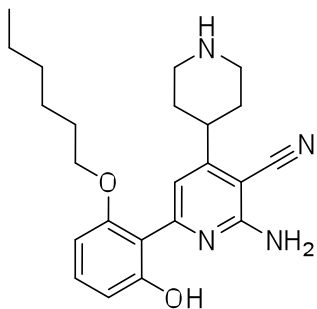
CAS 740792-29-4

IC₅₀ = 15 nM

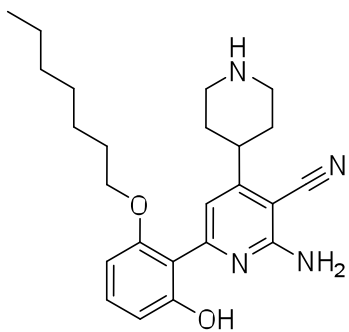


CAS 744217-92-3

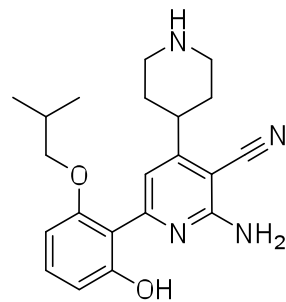
IC₅₀ = 20 nM



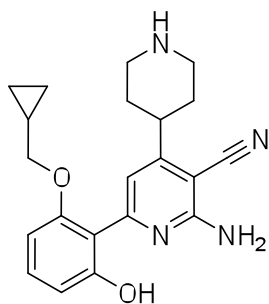
CAS 406208-63-7
 $IC_{50} = 25 \text{ nM}$



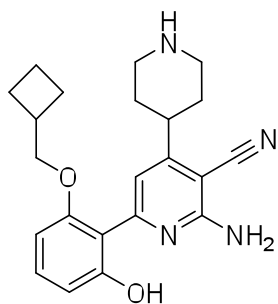
CAS 744217-93-4
 $IC_{50} = 50 \text{ nM}$



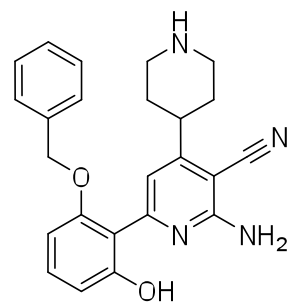
CAS 744217-94-5
 $IC_{50} = 15 \text{ nM}$



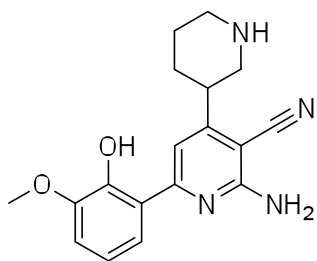
CAS 406208-42-2
 $IC_{50} = 8.5 \text{ nM}$



CAS 744217-54-6
 $IC_{50} = 12 \text{ nM}$

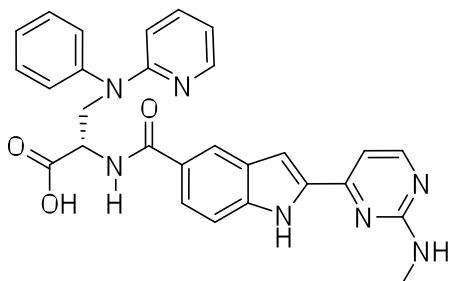


CAS 744217-95-6
 $IC_{50} = 110 \text{ nM}$



CAS 744217-80-9
 $IC_{50} = 20 \text{ }\mu\text{M}$

Haddad et al., 2005¹⁴

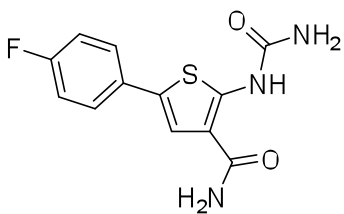


CAS 869796-50-9

IC₅₀ = 0.4 nM

compound 1

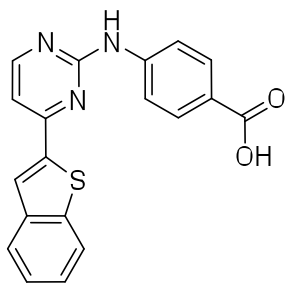
Podolin et al., 2003¹⁵



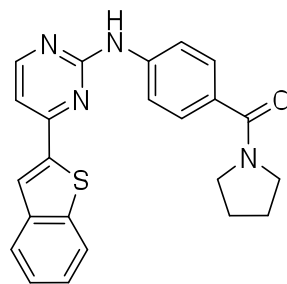
TPCA-1

CAS 507475-17-4

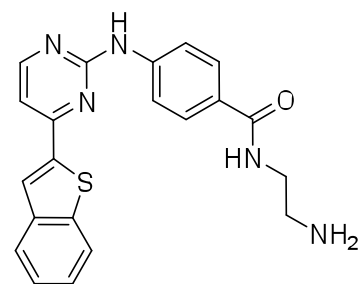
IC₅₀ = 17.9 nM



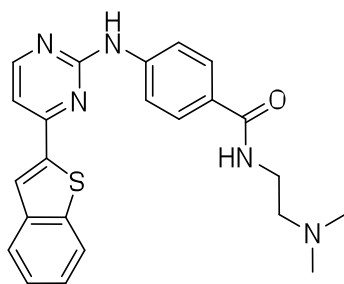
CAS 873225-30-0
IC₅₀ = 600 nM



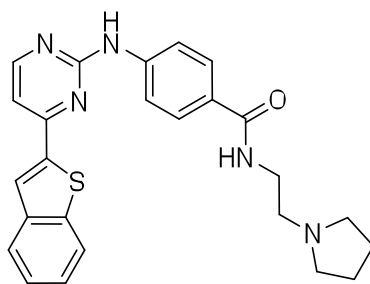
CAS 873225-40-2
IC₅₀ = 900 nM



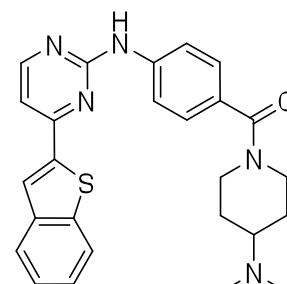
CAS 873225-41-3
IC₅₀ = 600 nM



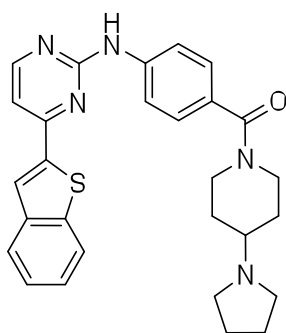
CAS 873225-42-4
IC₅₀ = 200 nM



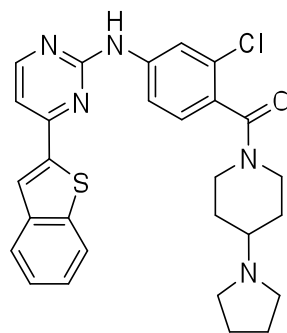
CAS 873225-44-6
IC₅₀ = 400 nM



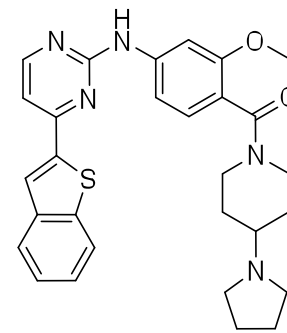
CAS 873225-45-7
IC₅₀ = 40 nM



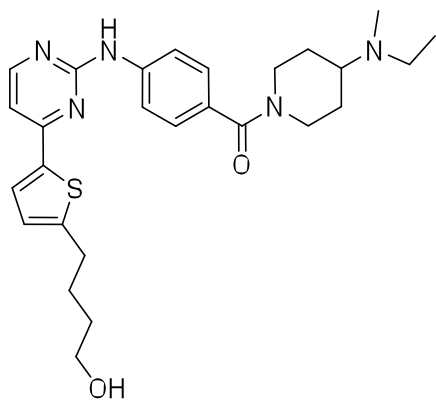
CAS 873225-46-8
IC₅₀ = 40 nM



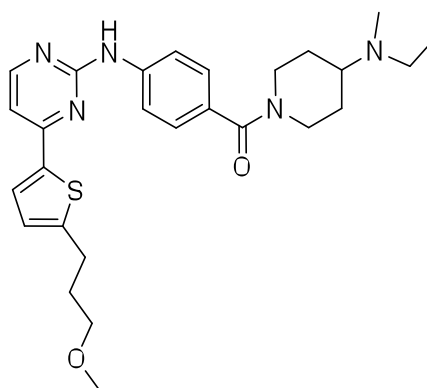
CAS 873225-47-9
IC₅₀ = 90 nM



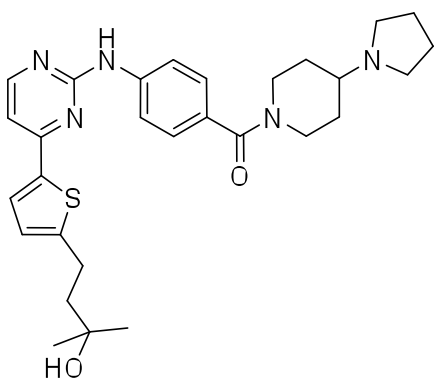
CAS 873225-48-0
IC₅₀ = 50 nM



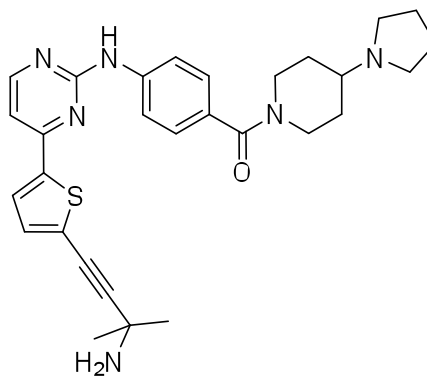
CAS 873225-56-0
 $IC_{50} = 25 \text{ nM}$



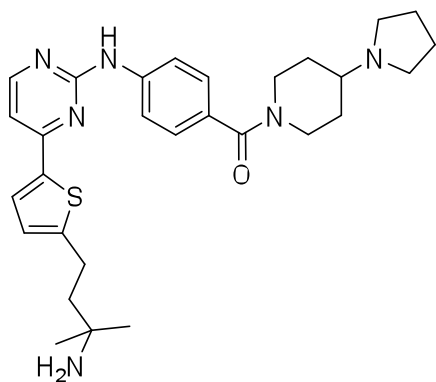
CAS 873225-57-1
 $IC_{50} = 100 \text{ nM}$



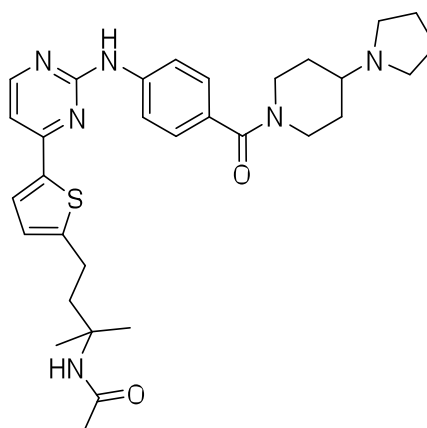
CAS 873225-58-2
 $IC_{50} = 50 \text{ nM}$



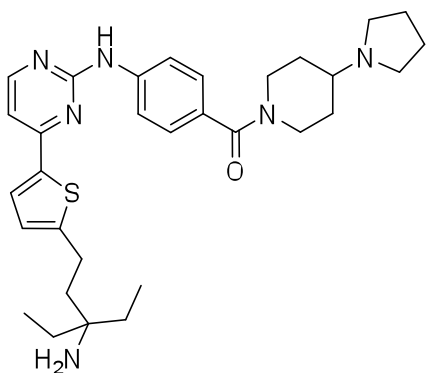
CAS 873225-59-3
 $IC_{50} = 150 \text{ nM}$



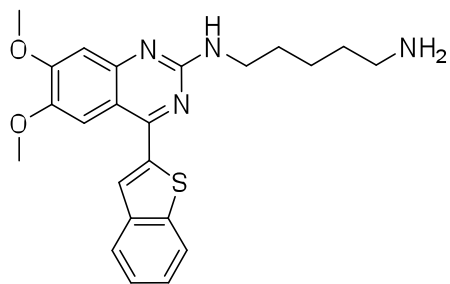
CAS 873225-60-6
 $IC_{50} = 40 \text{ nM}$



CAS 873225-61-7
 $IC_{50} = 150 \text{ nM}$

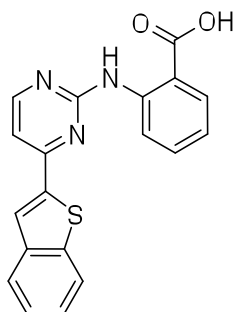


CAS 873225-62-8
 $IC_{50} = 60 \text{ nM}$

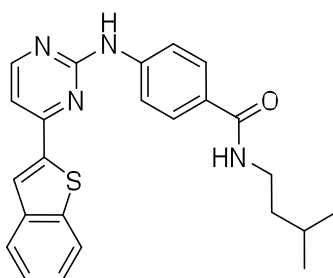


CAS -
 $IC_{50} = 30 \mu\text{M}$

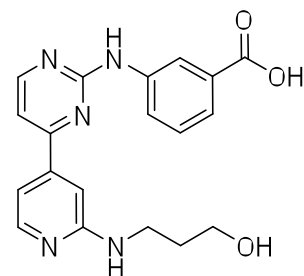
compound 6



CAS 873225-32-2
 $IC_{50} > 100 \mu\text{M}$

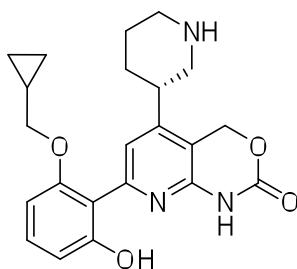


CAS 873225-43-5
 $IC_{50} > 100 \mu\text{M}$



CAS 164658-21-3
 $IC_{50} = 15 \mu\text{M}$

Ziegelbauer et al, 2005¹⁷



CAS 600734-02-9
 $IC_{50} = 2 \text{ nM}$

compound 2

2) Molecular docking of biologically active compound into a homology model of IKK- β

The homology model of IKK- β was available from the SWISS-MODELER repository.¹⁸⁻²⁰ Docking experiments were conducted using GOLD 3.1.²¹ A starting 3D geometry for compound **8** was generated with CORINA²², a commonly used 2D to 3D molecular structure converter. Afterwards, we selected the hinge region (Glu97) acceptor- (Cys99) donor- (Cys99) acceptor as essential constraints for the docking experiments. Lauria et al., who recently reported a docking-based molecular modeling study on IKK- β inhibitors, emphasized that the protein flexibility has to be accounted for in order to retrieve more reliable results.²³ Following these findings, we conducted induced-fit docking in GOLD by defining the gatekeeper residue Met96 as flexible.

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