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PATENT HIGHLIGHT

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# Pyridinonaphthyridinone Inhibitors of Type 2 Methionine Aminopeptidase

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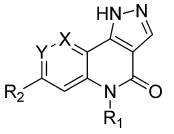
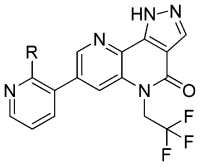
|---|---|---|---|
| **Title:** | Pyridinonaphthyridinone Inhibitors of Type 2 Methionine Aminopeptidase | | |
| **Patent/Patent Application Number:** | WO 2014/154586 A1 | **Publication date:** | October 2, 2014 |
| **Priority Application:** | EP 2013−305365 | **Priority date:** | March 25, 2013 |
| **Inventors:** | Guillo, N.; Martin, V. | | |
| **Assignee Company:** | Sanofi, Inc. | | |
| **Disease Area:** | Fibrosis, cancer | **Biological Target:** | Type 2 Methionine Aminopeptidase (METAP2) |

**Summary:** The present application claims a series of pyridinonaphthyridinone as inhibitors of METAP2. The compounds described here are potentially useful in the treatment of a wide range of disorders such as pulmonary and hepatic fibrosis, age-related mascular degeneration, psoriasis, autoimmune diseases, and cancer.

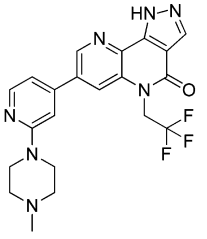
**Important Compound Classes:**



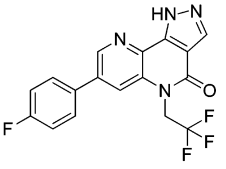
**Key Structures:**



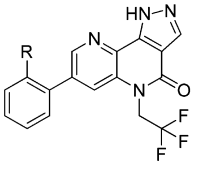
R = Cl, **Compound 1**
R = H, **Compound 2**



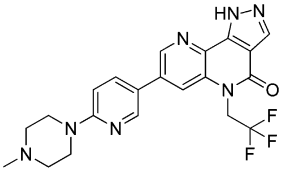
**Compound 3**



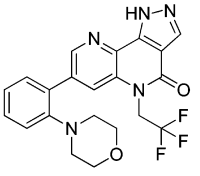
**Compound 4**



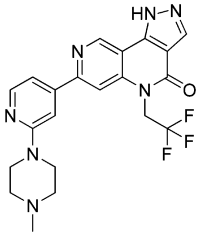
R = $CH_3$, **Compound 5**
R = $CF_3$, **Compound 6**
R = $CONH_2$, **Compound 11**
R = $SO_2NHMe$, **Compound 19**
R = $NHSO_2Me$, **Compound 22**



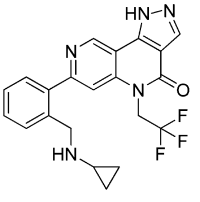
**Compound 31**



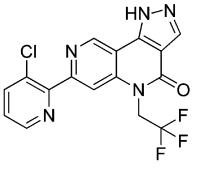
**Compound 32**



**Compound 40**



**Compound 47**



**Compound 53**

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**Biological Assay:** The enzymatic activity of the compounds was evaluated in a two-step procedure. First the compound is incubated with dialyzed human MetAP2 and the substrate Met-Pro-Arg-pNa. The N-terminal methionine can be cleaved with MetAP2 to obtain the Pro-Arg-pNa substrate. In the second step the *para*-nitroanilide (pNa) chromophore is released with a second peptidase.

**Pharmacological Data:**

Enzymatic assay

| Compound | hMETAP2 $IC_{50}$ (μM) | Compound | hMETAP2 $IC_{50}$ (μM) |
|---|---|---|---|
| **1** | 11 | **19** | 4 |
| **2** | 64 | **22** | 8 |
| **3** | 24 | **31** | 5 |
| **4** | 234 | **32** | 187 |
| **5** | 3 | **40** | 11 |
| **6** | 20 | **47** | 21 |
| **11** | 1020 | **53** | 13 |

**Synthesis:** The synthesis and biological activity of sixty-eight compounds are described.

## AUTHOR INFORMATION

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### Notes
The authors declare no competing financial interest.