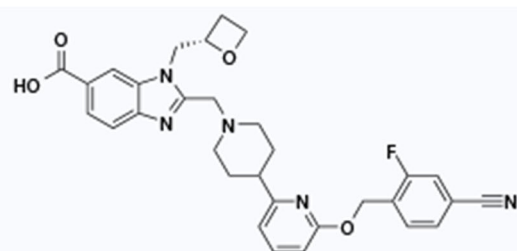
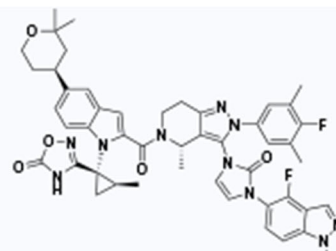


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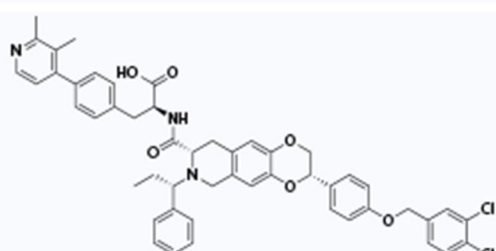

Glucagon-like peptide-1 (GLP-1) is secreted from intestinal L cells, and it promotes insulin secretion in a glucose-dependent manner by binding to the GLP-1 receptor (GLP-1R)^[1]. GLP-1R belongs to a family of G-protein coupled receptors and it is highly expressed on pancreatic β cells and large ducts. Activating the GLP-1R has been shown to have beneficial effects on insulin secretion and the maintenance of beta cell glucose sensing, transcription, synthesis, proliferation, and survival. GLP-1R agonists are currently being investigated in connection with type 2 diabetes, obesity, and NASH. GLP-1R agonists include peptides, such as exenatide, liraglutide, and dulaglutide, that have been approved by FDA for the management of type 2 diabetes. Such peptides are predominantly administered by subcutaneous injection and they have poor patient compliance compared to oral administration. Therefore, as an alternative, small molecule GLP-1R agonists can provide a more standard drug formulation and a simpler method of administration. To date, several small molecule GLP-1R agonists have entered into clinical trials^[2-8].



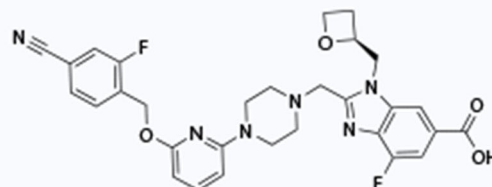
PF-06882961 (Phase II)
small molecule GLP-1R agonist



LY-3502970 (Phase II)
small molecule GLP-1R agonist



TT-OAD2
small molecule GLP-1R agonist



Example 23 (WO2022109182A1)
small molecule GLP-1R agonist

A series of building blocks will be used as molecular fragments in the design of small molecule GLP-1R agonists.

[1] Bioorganic & Medicinal Chemistry (2021), 52, 116496.

[2] Journal of Medicinal Chemistry (2021), 64, 6, 3439–3448.

[3] Journal of Medicinal Chemistry (2022), 65, 12, 8208-8226.

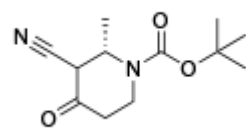
[4] Journal of Medicinal Chemistry (2020), 63, 5, 2292-2307.

[5] European Journal of Medicinal Chemistry (2015), 103, 175-184.

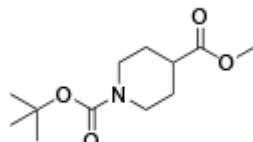
[6] European Journal of Medicinal Chemistry (2022), 233, 114214.

[7] Journal of Medicinal Chemistry (2022), 65, 7, 5449–5461.

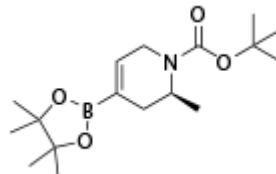
[8] WO2022109182A1.



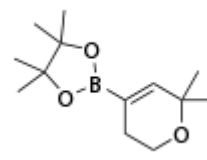
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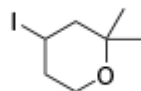
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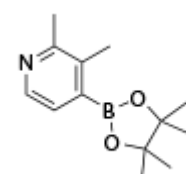
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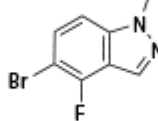
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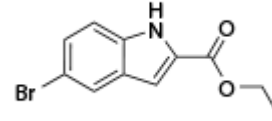
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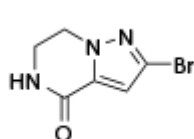
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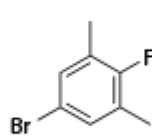
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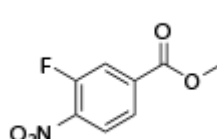
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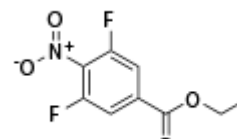
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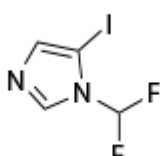
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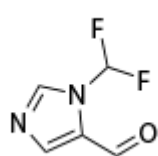
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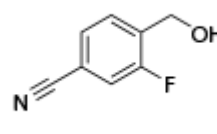
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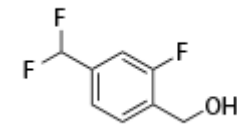
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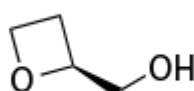
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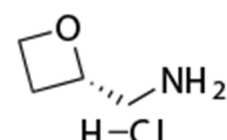
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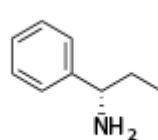
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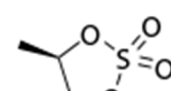
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