Glucocorticoid Receptor Agonist

BI653048

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Summary

BI 653048 is a "dissociated" GR agonist (displaying different transcriptional regulatory profiles between gene transrepression and transactivation).
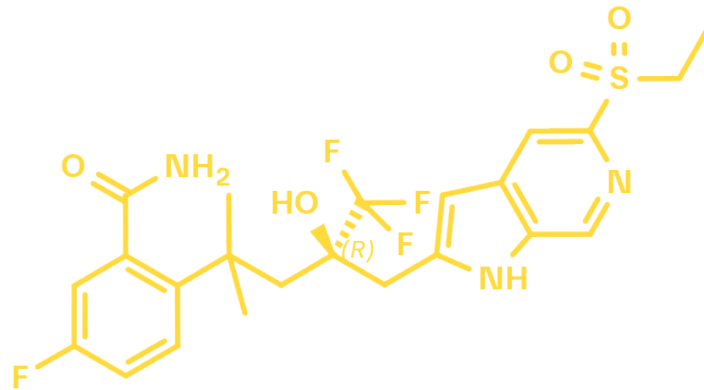
Chemical Structure

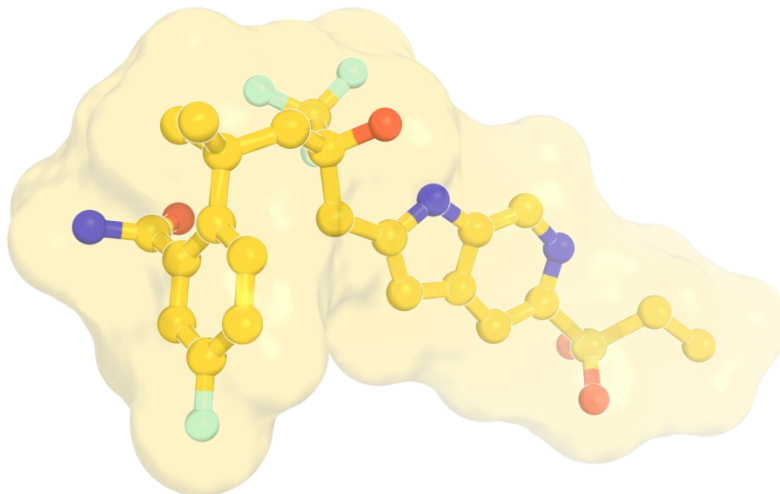**Figure 1: 2D structure of BI 653048, a Glucocorticoid Receptor Agonist**


Figure 2: 3D structure of BI 653048

Highlights

BI-653048 is a dissociated GR agonist, i.e., it displays different regulatory profiles between gene transrepression and transactivation. It has good selectivity against related nuclear receptors (> 100-fold), such as MR or PR, and good drug-like properties. However, this compound is not suitable for *in vivo* evaluation in standard preclinical mouse models, as it showed species selectivity with reduced functional transrepression potency in mice.

Target information

Cortisol and the related cortisone and corticosterone are steroid hormones that are referred to as glucocorticoids (GCs) and bind to the glucocorticoid receptor (GR), which belongs to a large family of transcription factors, the superfamily of nuclear hormone receptors. GCs play an important role in the regulation of the immune system and therefore are widely used in the treatment of inflammatory and immune diseases such as rheumatoid arthritis, asthma, allergy, and sepsis. Synthetic GCs, which differ from cortisol in their pharmacokinetics and pharmacodynamics, have been created with dexamethasone and prednisolone being among the most extensively used anti-inflammatory agents. However, because of harmful dose-limiting side effects and the occurrence of glucocorticoid resistance, the use of these drugs is limited. Side effects include weight gain, hypertension, muscle weakness, skin thinning, diabetes, and the most troublesome GC-induced osteoporosis leading to a weakening of the trabecular bone, which causes a significant increase in the risk of spine, hip, and rib fracture. Upon binding of GCs to GR, a conformational change is provoked leading to the release of GR from the chaperone complexes and unmasking of nuclear localization signals followed by translocation of the GR—ligand complex to the nucleus. There, it is thought to directly and indirectly induce the expression of a few hundred genes, which is largely cell-type specific. The precise molecular mechanism is highly complex and, despite an impressive amount of research, still only partially understood. However, a simplistic hypothesis, which is based on a series of experiments, has become broadly accepted among researchers aiming at GCs with reduced side effects. This hypothesis attributes the anti-inflammatory effects of GCs to the inhibition of gene transcription, referred to as transrepression, while making the activation of transcription, called transactivation, responsible for the majority of side effects. Mechanistically it was rationalized that transrepression involves the GR—ligand complex indirectly in the transcription process through its interaction in a monomeric form with transcription factors such as NF-κB and AP-1 resulting in the down-regulation of key cytokine inflammatory mediators such as TNF-α, IL-1, IL-2, and IL-6. The transactivation pathway directly involves homodimers of GR recognizing GR response elements (GREs) on the DNA resulting in the transcription of genes. While this hypothesis is experimentally poorly supported and partially even contradicted, it served as an appealing working model for drug discovery programs over the past decade. Several companies have invested intense research in the quest of identifying functionally selective, so-called "dissociated" synthetic glucocorticoids with the goal of offering a therapeutic advantage over currently marketed GCs[1].
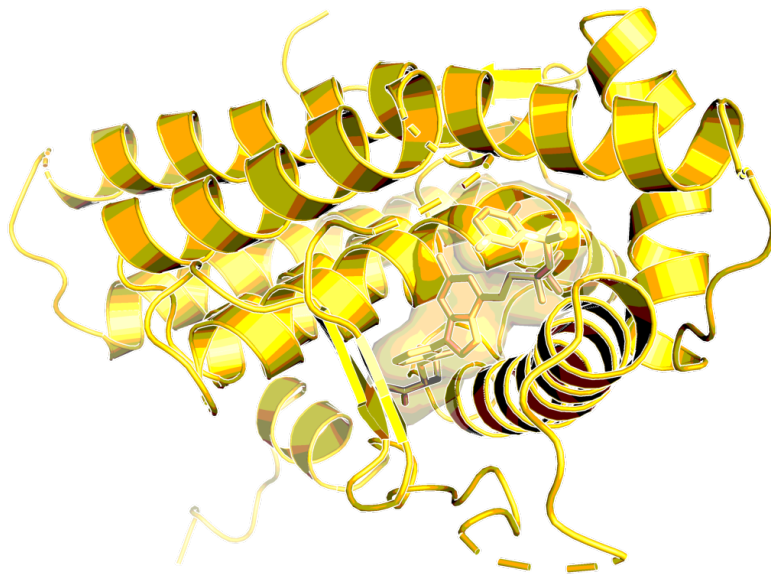
Figure 3: Human glucocorticoid receptor with bound agonist (PDB code: 3k23)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BI-653048	BI-3047
MW [Da, free base][a]	515.5	515.5
GR (IC_{50}) [nM]	55	>2,000
IL-6 (IC_{50}) [nM]	23	n.a.
IL-6 (IC_{50}) max. eff. [%][b]	88	n.a.
MMTV max. eff. [%][b]	33	n.a.
OC max. eff. [%][b]	39	n.a.

[a] For the salt form you will get, please refer to the label on the vial and for the molecular weight of the salt, please refer to the FAQs

[b]Maximum efficacy at the highest tested concentration compared to dexamethasone, defined at 100%; maximum concentration tested is 2 µM.

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-653048	BI-3047
logD @ pH 7	2.7	2.9
Solubility @ pH 6.8 [µg/mL]	30.7	n.a.
Caco-2 permeability AB @pH7.4 [$*10^{-6}$ cm/s]	6	n.a.
Caco-2 efflux ratio	3.5	n.a.
Microsomal stability (human/rat) [% Q_H]	13 / <6	22 / n.a.
Hepatocyte stability (human/rat/dog) [% Q_H]	13 / 23 / <7	n.a.
Plasma Protein Binding (human/rat/dog) [%]	91.8 / 96.1 /97.4	n.a.
hERG (IC_{50}) [µM]	>30	n.a.
CYP 1A2 [µM]	>50	n.a.
CYP 2D6 [µM]	41	n.a.
CYP 2C9 [µM]	12	n.a.
CYP 2C19 [µM]	9	n.a.
CYP 3A4 [µM]	8	n.a.

[a] Assay conditions can be downloaded free of charge from pubs.acs.org

In vivo DMPK parameters

BI 653048	RAT
Clearance [%Q_H][a]	16.6
Mean residence time after *i.v.* dose [h]	2.6
t_{max} [h][b]	1.7
C_{max} [nM][b]	1923
F [%]	50
V_{ss} [L/kg][a]	1.8

[a] *i.v.* dose: 1 mg/kg
[b] *p.o.*. dose: 5 mg/kg

In vivo pharmacology

Species selectivity of this subseries of compounds precluded a pharmacological evaluation of BI 653048 in standard preclinical *in vivo* mouse models. Translation of *in vitro* dissociation markers to preclinical *in vivo* mouse models had been previously established with tool compounds[2].

BI 653048 was tested in a 9-day type II collagen-induced arthritis model in rats at 3, 10, and 30 mg/kg qd *po* in 30% cremophor to guide human efficacious concentration projections. Animals treated with the low dose (3 mg/kg) of BI 653048 had nonsignificant decreases for all measured histology parameters (ankle inflammation, pannus formation, cartilage damage, and bone resorption)[1].

Middose (10 mg/kg) animals had significantly decreased pannus and bone resorption (33%) as well as summed scores (27%), while all parameters were significantly decreased (87–96%) in the high dose (30 mg/kg) group. The ED_{50} value for the summed scores was 14 mg/kg. No side effect related parameters were feasible to be evaluated in this shorter duration model[1].

Negative control

BI-3047 shows no activity on GR (CR IC$_{50}$ > 2 µM).
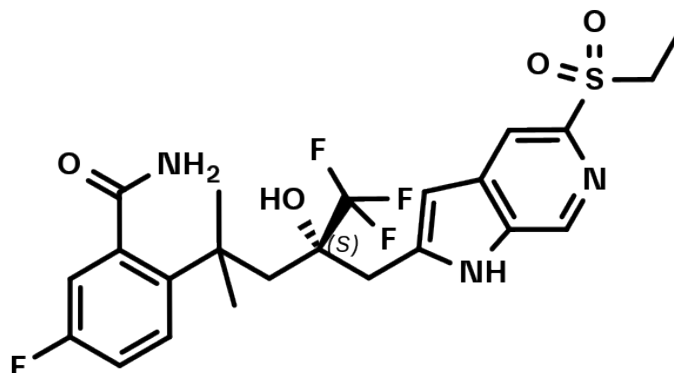

Figure 4: Chemical structure of the negative control BI-3047

Selectivity

Screened against related nuclear receptors (PR, MR, ER, AR): > 100 fold selectivity achieved

A Eurofins Safety Panel 44™ panel was performed and did not give strong hits: %CTRL >75% for all 49 targets tested @ 10 µM. The data can be downloaded from this platform.

SELECTIVITY DATA AVAILABLE	BI-653048	BI-3047
SafetyScreen44™ with kind support of **eurofins**	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

See reference 3

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

1. Harcken C., Riether D., Liu P., Razavi H., Patel U., Lee T., Bosanac T., Ward Y., Ralph M., Chen Z., Souza D., Nelson R. M., Kukulka A., Fadra-Khan T. N., Zuvela-Jelaska L., Patel M., Thomson D. S., Nabozny G. H. Optimization of drug-like properties of nonsteroidal glucocorticoid mimetics and identification of a clinical candidate *ACS Med Chem Lett* **2014**, 5,1318-1323. DOI:10.1021/ml500387y, PubMed: 25516791.

2. Harcken C., Riether D., Kuzmich D., Liu P., Betageri R., Ralph M., Emmanuel M., Reeves J. T., Berry A., Souza D., Nelson R. M., Kukulka A., Fadra T. N., Zuvela-Jelaska L., Dinallo R., Bentzien J., Nabozny G. H., Thomson D. S. Identification of Highly Efficacious Glucocorticoid Receptor Agonists with a Potential for Reduced Clinical Bone Side Effects *J Med Chem* **2014**, 57, 1583-1598. DOI: 10.1021/jm4019178, PubMed: 24506830.

3. Sundahl N., Bridelance J., Libert C., De Bosscher K., Beck I. M. Selective glucocorticoid receptor modulation: New directions with non-steroidal scaffolds *Pharmacol Ther* **2015**, 152, 28-41. DOI: 10.1016/j.pharmthera.2015.05.001, PubMed: 25958032.