Technology bulletin

CSIR-Indian Institute of Chemical Biology, India

# Potent inhibitors of the toll-like receptor, TLR9

## A series of novel and potent inhibitors of toll-like receptor 9 (TLR9), with potential application in autoimmune disease and metabolic syndrome.

- ❑ Potent (nanomolar) inhibitors of toll-like receptor 9: 'ABODINIBS'
- ❑ Demonstrated efficacy in human immune cells and pharmacokinetics in preclinical rodent model

## Challenge/Application domain

Activation of toll-like receptors (TLRs) on immune cells is one of the critical mechanisms for self-nonself discrimination by the host immune response[1]. Interestingly, aberrant TLR9 activation is implicated in the pathogenesis of a number of autoimmune diseases[2] (viz. psoriasis, systemic lupus, scleroderma, rheumatoid arthritis, type 1 diabetes etc.) as well as in different components of metabolic syndrome[3] (obesity-associated type 2 diabetes, fatty liver disease, atherosclerosis). TLR9 is established as an important therapeutic target in these different clinical contexts. But inhibitors of TLR9 are yet to be available for clinical use.

## Technology

The present invention relates to a lead series of small molecule compounds for inhibiting TLR9[4,5], developed through rational design driven by well characterized SAR in human primary immune cells (Table 1). The lead series includes molecules with oral bioavailability, documented target-binding, favourable pharmacokinetics and in vivo efficacy for TLR9 antagonism in preclinical rodent models.

| Compound Code | $IC_{50}$ (nM) for human TLR9 |
|---|---|
| ABODINIB-4.11 | 50 |
| ABODINIB-2.83 | 20 |
| ABODINIB-4.119 | 40 |
| ABODINIB-3.73 | 18 |
| ABODINIB-3.79 | 27 |
| ABODINIB-3.67 | 77 |
| ABODINIB-3.75 | 22 |
| ABODINIB-4.81 | 26 |
| ABODINIB-3.99 | 15 |
| ABODINIB-3.93 | 41 |

## Opportunity

**CSIR-Indian Institute of Chemical Biology** is seeking to transfer the technology of this advanced lead series of TLR9 inhibitors to an pharmaceutical industry entity (with global footprint and past experience with clinical trial for drugs toward global regulatory approval for human use) for further preclinical development and nomination of clinical candidate/s for evaluation in clinical trials.

### References


1. Gilliet Met al., Nat Rev Immunol, 2008.
2. Ganguly D et al., Nat Rev Immunol, 2013.
3. Ganguly D, Trends Immunol, 2018.
4. Roy S et al., Eur J Med Chem, 2017.
5. Talukdar A et al., Patent WO2017163264 A1.


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