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Balinatunfib: A Clinical Oral Small Molecule TNFα Inhibitor

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Most diseases are accompanied by an inflammatory response, making effective pharmacological control highly desirable. Tumor necrosis factor alpha (TNFα) is a key cytokine driving inflammatory and autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease. Although biological TNFα inhibitors revolutionized treatment, they have drawbacks including lacking blood–brain barrier penetration, parenteral administration, and immunogenicity. Recent studies highlight the potential of small-molecule approaches to target TNFα by stabilizing an asymmetrical, receptor-incompetent trimer conformation. Balinatunfib (also known as SAR441566) is an orally available small molecule designed to exploit this mechanism, thereby preventing TNFα from effectively binding to its receptors. In preclinical models, balinatunfib reduces inflammation comparably to biologic therapies, yet avoids the complexities of large protein therapeutics. This allosteric strategy involves capturing a sampled but distorted state of TNFα, thereby blocking receptor clustering and downstream proinflammatory signaling. The oral route of administration confers practical advantages in terms of patient compliance and could facilitate drug access to sites traditionally less amenable to biologics, such as the central nervous system. By demonstrating that small molecules can achieve high-affinity, conformation-based inhibition of TNFα, balinatunfib, and related compounds may result in a new area of orally administered therapies that advance the management of TNFα-mediated diseases.

1. Early Attempts and Breakthroughs

TNFα, a pleiotropic cytokine orchestrating myriad proinflammatory and immunoregulatory processes, has long[1] attracted therapeutic interest for the management of autoimmune and inflammatory diseases.[2] There is also increasing evidence that the TNF/TNFR2/TNFR1 system plays an important role in the immune aspects of cancer.[3–5] Since the 1970s, the field's understanding of TNFα has evolved alongside dramatic advancements in recombinant protein and antibody technologies.[6] Most prominently, the emergence of anti-TNF biologics—such as infliximab and adalimumab—radically transformed care for rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, and other TNF-driven pathologies. Despite these gains, significant challenges remain. Biologic therapies are expensive, administered parenterally, subject to immunogenic responses, and limited in crossing physiological barriers like the blood–brain barrier. Consequently, the dream of an orally bioavailable small-molecule TNFα inhibitor—once thought out of reach owing to TNFα's extensive and largely flat protein–protein interaction interface—has spurred numerous research efforts over the past two decades. In the early 2000s, researchers identified SPD-304 (**1**), a compound that bound TNFα and induced partial trimer destabilization, thereby hinting that a small-molecule strategy could potentially disrupt TNFα's receptor-binding interface.[7] However, that early compound and similar leads were difficult to optimize because they targeted a large, symmetric trimeric interface and lacked drug-like tolerability in vivo. A transformative step emerged when investigators demonstrated that TNFα transiently samples an asymmetric trimer conformation, which could be stabilized with designed fragments (e.g., **1**) to inhibit the cytokine allosterically without directly blocking the receptor-contacting region. This concept was showcased in major publications describing how small molecules (**1**–**4**) could "lock" TNFα into a nonsignaling shape.[8–11] Researchers at various institutions, including AbbVie and Bristol Myers Squibb, then applied fragment-based drug design to identify potent, selective inhibitors that bound deep within the intermonomeric pockets of TNFα, and subsequent scaffold-hopping yielded compounds efficacious in murine arthritis models. These achievements ultimately validated the possibility of oral TNFα inhibitors with favorable absorption, tissue penetration, and target specificity, including minimal cross-reactivity with other TNF superfamily members (**Figure 1**).

2. First in Class Small Molecule TNFa Inhibitor: Balinatunfib

The culmination of these efforts is balinatunfib, also referred to as SAR441566, the first oral small-molecule TNFα inhibitor currently

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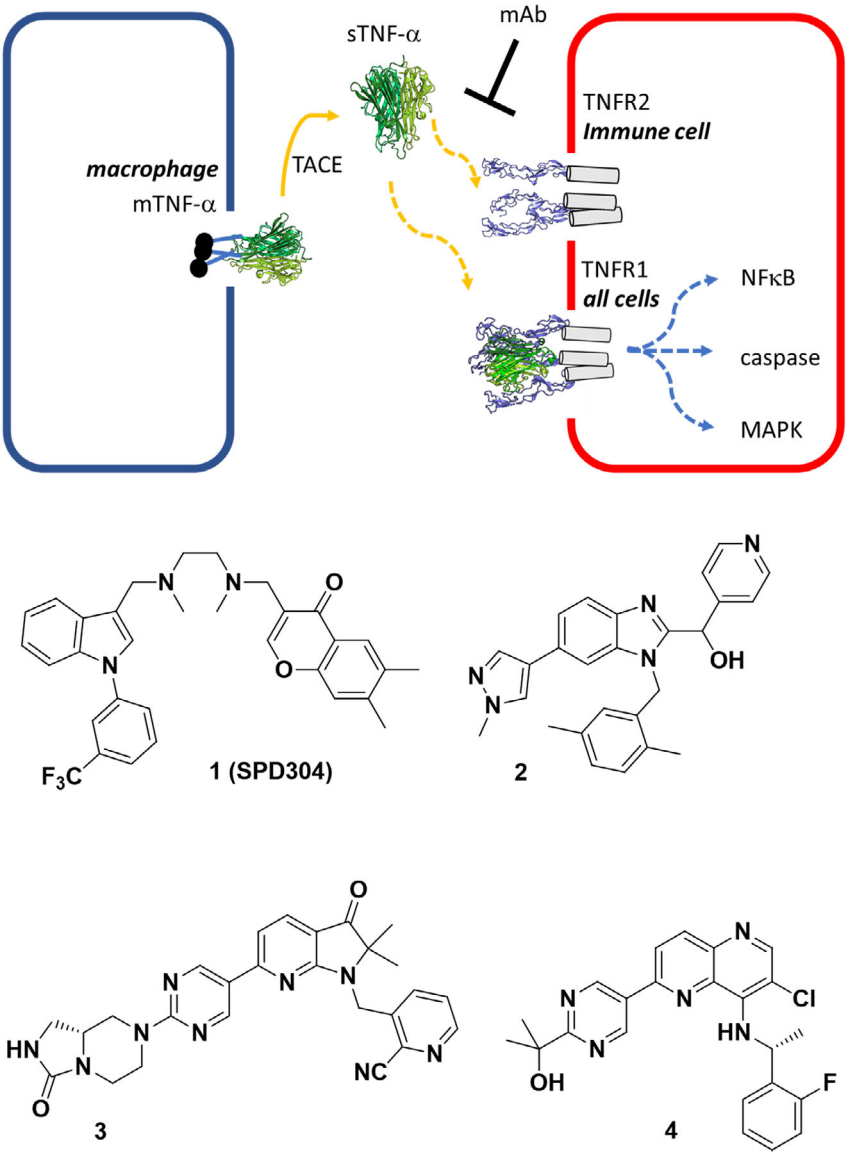

Figure 1. TNFα's role in inflammation and autoimmune disease (adapted from ref. [12]) and early small molecule attempts to directly inhibit TNFα.

evaluated in several human clinical trials (e.g., NCT06867094, NCT06637631, NCT06073093) for different indications. Developed through a collaborative initiative involving Sanofi and UCB, it stabilizes an asymmetrical form of soluble TNF alpha, preventing the higher-order receptor clustering required for TNF-mediated signaling.[1] Surface plasmon resonance (SPR) measurements demonstrated a dissociation constant (K_D) of 15.1 nM for the compound's binding to human TNFα, indicating high-affinity engagement and thus a long residence time ($t_{1/2} \approx 9$ h). This binding event stabilizes an asymmetrical form of the TNFα trimer, rendering the cytokine incapable of recruiting sufficient receptor subunits for proinflammatory signaling. It appears that balinatunfib is binding in a similar way and into the same pocket in the TNFα trimer than previously reported inhibitors (**Figure 2**C,D). A docking model of balinatunfib to TNFα indicates several pi stacking interactions with tyrosine and hydrogen bondings with tyrosine-OH and a backbone hydrogen bonding. Further in vitro assays evaluated balinatunfib's efficacy in zymosan-stimulated human whole blood, where its half-maximal inhibitory concentration (IC_{50}) was 35 nM. Additional ELISA-based occupancy studies revealed that balinatunfib could fully occupy TNFα at nanomolar concentrations, underscoring the potent inhibition of the cytokine in a physiologically relevant context. Pharmacokinetic profiling indicated strong tissue penetration and acceptable oral bioavailability, partially attributed to the molecule's physicochemical properties (including favorable distribution and a measured half-life of around nine hours at the target site). In vivo efficacy was tested in a collagen-induced arthritis (CIA) mouse model. Oral dosing regimens of balinatunfib at 10 and 30 mg kg^{-1} led to significant reductions in disease scores, comparable to an anti-TNF antibody used as a positive control. High-resolution microcomputed tomography confirmed that treated animals exhibited improved bone parameters, illustrating the compound's biologic-like impact on joint integrity. Collectively,

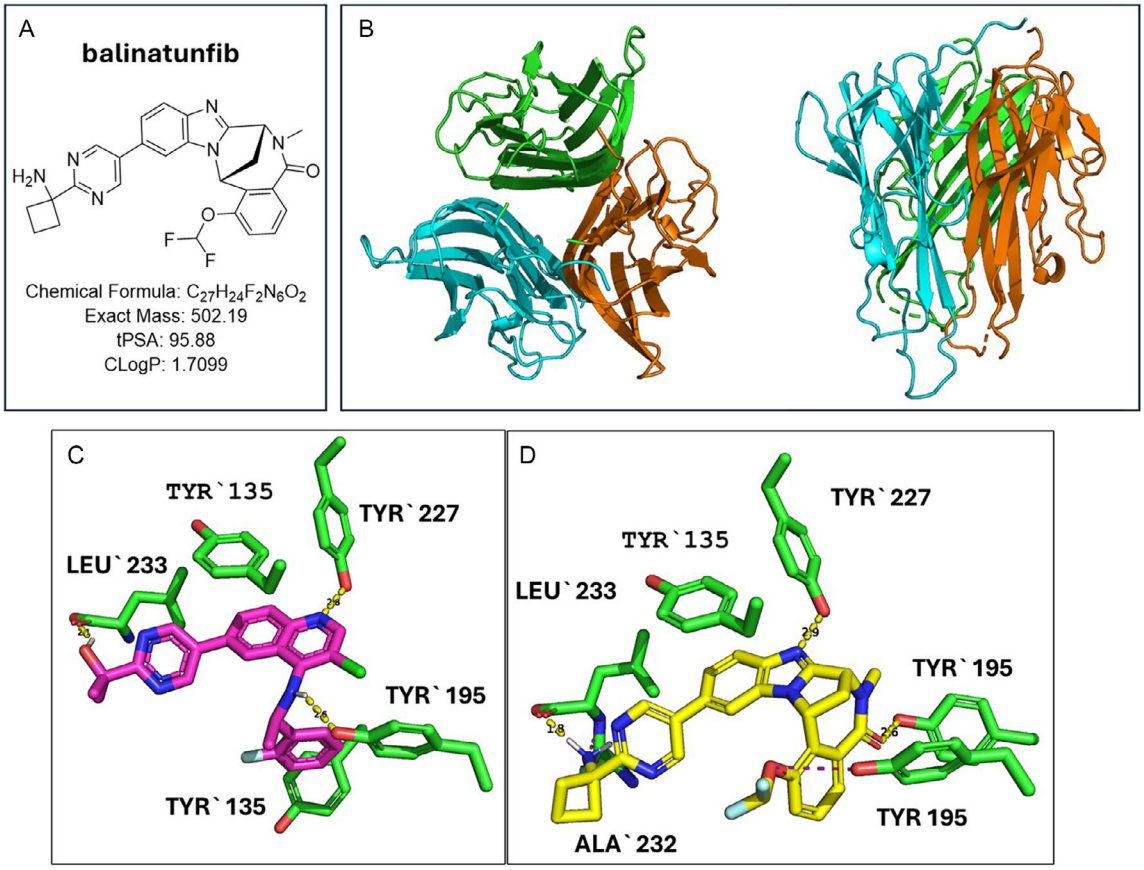

Figure 2. Balinatunfib—a first in class low molecular weight TNFα inhibitor. A) 2D structure of balinatunfib and some properties. An interesting feature of the molecule is its bicyclic stiff architecture which might contribute to its drug-like properties. B) TNFα trimer upside down and side-on view exemplifying the 3-fold symmetry. D) Docking model of balinatunfib (pink sticks) bound to TNFα (green sticks) in comparison to C) compound **4** (magenta sticks, PDB ID 7JRA).[9]

these findings position balinatunfib as a promising oral TNFα inhibitor with substantial potential to match established biologics while overcoming some limitations of injectable protein therapies. If early-phase clinical results prove favorable, balinatunfib could eventually become a more convenient and less immunogenic "anti-TNF pill." Its small-molecule nature may also allow penetration of physiological barriers that biologics cannot overcome, prompting further investigations into chronic inflammatory settings such as neurodegenerative disorders in which TNFα might have an important role.

Looking ahead, researchers are exploring whether balinatunfib's safety and efficacy can be extended to other diseases, including inflammatory bowel disease and neuroinflammatory syndromes. Even so, as with all forms of TNFα blockade, the risk of infections like tuberculosis calls for vigilant postmarketing surveillance once broader clinical usage begins. Pricing and accessibility are also set to shape the clinical impact of these agents, although reduced manufacturing complexity for oral therapies may mitigate some cost barriers. There is further interest in the potential for combination regimens that unite a rapidly titratable oral anti-TNF agent with other immunomodulatory drugs, including Janus kinase (JAK) inhibitors or interleukin-6 (IL-6) antagonists, to fine tune treatment strategies for autoimmune diseases. From the earliest conceptual attempts to destabilize the TNFα trimer to the more nuanced approach of immobilizing the cytokine in a nonfunctional conformation, the field has progressed toward oral therapeutics that challenge conventional notions of what small molecules can accomplish. Balinatunfib's preclinical performance and its transition into clinical development highlight the power of structure-based design, conformational selection, and fragment-growth methodologies. Should ongoing and upcoming studies confirm its promise, an orally administered agent with biologic-like efficacy could transform chronic inflammatory disease management. Furthermore, the potential to cross the blood–brain barrier underscores how a once "undruggable" target may yet be confronted by a new generation of small molecules that reshape the therapeutic landscape.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared

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