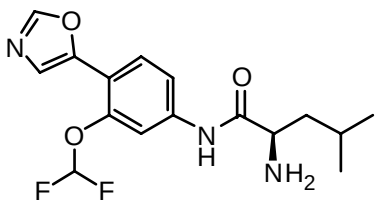
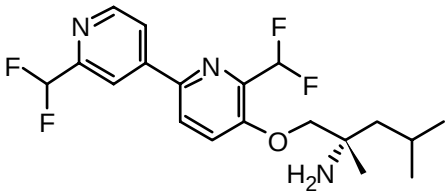
CRIPS Digest

Discovery of Biaryl Alkyl Amides and Biaryl Alkyl Ethers as AAK1 Inhibitors for the Treatment of Neuropathic Pain

Adaptor-associated protein kinase 1(AAK1) is a serine/ threonine kinase, from the family of NUMB associated kinases (NAKs). It regulates the clathrin mediated endocytosis by phosphorylating the Thr-156 of the μ2 subunit of the adaptor protein complex 2 (AP-2). AAK1 is commonly expressed in the spinal cord and brain. It was identified as a potential therapeutic target for the treatment of neuropathic pain based on the screening of 3097 mouse knockout lines in hot-plate and formalin assay. For this, NSAIDs, TCAs, SNRIs, and gabapentinoids are recommended as first-line treatments and weak opioid analgesics such as tramadol and tapentadol are recommended as second-line treatment. A library of clinically used kinase inhibitors was screened from which small repurposed drugs such as baricitinib, momelotinib, lestaurtinib, nintetanib, fedratinib, sunitinib, etc were identified as AAK1 inhibitors. Several other selective inhibitors such as LP-935509, LP-922761, LP-927443, BMS-901715, BMT-090605, BMT-124110 were identified. AAK1 has also been studied as a potential drug target for the treatment of SARS-CoV-2, dengue virus and Ebola virus. The authors carried out the SAR studies of a novel class of bi(hetero)aryl ethers which was inspired from their own previous work on biaryl amide-based compounds, a highly selective and potent AAK1 inhibitor BMS-9861762/ LX-9211 etc. was identified which has entered into phase II human clinical trials for diabetic peripheral neuropathic pain and post-herpetic neuralgia. (J. Med. Chem.2021, 64, 11090; J. Med. Chem. 2022, 65, 4457; J. Med. Chem. 2022, 65, 4534).



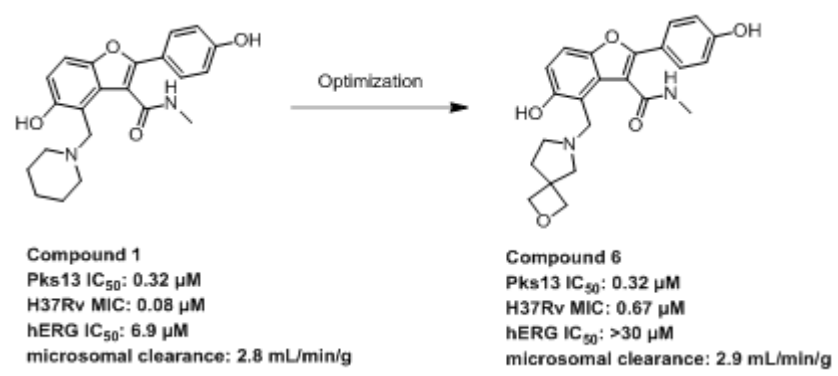
Bi(hetero)aryl alkyl amide



BMS-986176/LX9211
Bi(hetero)aryl aryl alkyl ethers

Optimization of TAM16, a Benzofuran That Inhibits the Thioesterase Activity of Pks13; Evaluation toward a Preclinical Candidate for a Novel Antituberculosis Clinical Target.

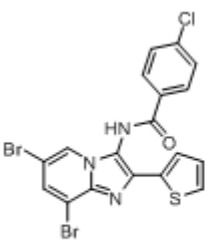
Tuberculosis (TB) is an infectious disease caused by the bacteria Mycobacterium tuberculosis that mostly affects the lungs. Every year, more than 10 million individuals are diagnosed with tuberculosis, and 1.4 million of them die as a result of the disease. The typical TB treatment plan includes first-line medications isoniazid (INH), rifampicin (R), pyrazinamide (Z), and ethambutol (E) administered over 6 months of directly observed treatment short strategy (DOTS) with a cure rate of 90 to 95 percent. Despite the ability to provide anti-TB treatment quickly (DOTS), the fight against tuberculosis continues since drug resistance is rising. Mycolic acids are vital lipid components of the mycobacterial cell membrane that are required for the survival and pathogenicity of the Mycobacterium genus. Their production is a complex process that necessitates the coordination of approximately 20 enzymes. The clinical use of first-line drugs isoniazid and ethionamide, as well as the preclinical efficacy of previously reported Mmpl3 inhibitors such as indoleamides and adamantylureas, have all demonstrated that inhibiting pathways related to mycolic acid synthesis is a viable approach for anti-TB drug discovery. Polyketide synthase 13 (Pks13) was identified as the main enzyme involved in the final assembly stage of mycolic acid production by Claisen-type condensation. Aggarwal and colleagues have revealed new



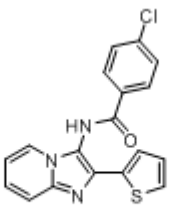
Benzofuran series compounds as Pks13-thioesterase (TE) domain inhibitors of Mycobacterium tuberculosis. Many drugs having lipophilic amine residue interact with the hERG channel and exhibit cardiotoxicity. When the first piperidine moiety containing lead chemical 1 was examined for hERG susceptibility, it demonstrated high potency in vitro Q-patch testing, indicating a risk of cardiotoxicity. (IC_{50}=6.9 μM) The inhibition of Pks13 was dramatically decreased when the piperidine moiety was substituted with a cyclohexyl or phenyl group. Keeping these considerations in mind, other less basic moieties were explored for Pks13 assay, and a species with 2-oxa-6-azaspiro[3.4]-octane moiety demonstrating the best overall features of the series has been identifies. Despite improvements in the hERG liability in vitro, compound 6 (IC_{50} >30 μM) still produced cardiac abnormalities when tested in ex vivo cardiotoxicity models. While there have been improvements, the Cardiac profiler panel found that hERG channel blockage remained a potential hazard. This series of benzofurans has been associated with both direct target binding and off-target cardiovascular harm owing to hERG channel blocking by a lipophilic amine, hence further series development was suspended due to safety concerns. Pks13 is, however, an appealing potential target for antitubercular medicines due to its in vivo activity ability to encourage the establishment of diverse chemotypes.(J. Med. Chem. 2022, 65, 409).

Design and synthesis of imidazo[1,2-a]pyridine-3-carboxamide derivatives as GABA agonists

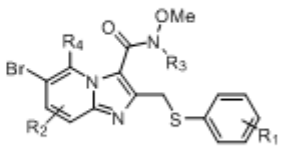
Targeting δ-selectivity for the GABA receptors, many active molecules were reported. Delta subunit containing GABA receptors play crucial role in CNS related diseases for example alcoholism, epilepsy, and major depression disorders. Imidazo[1,2-a]pyridine containing various drugs and drug candidate are already available in the market in which, DS1 and DS2 exhibit significant δ selectivity. DS1 is known drug which possesses positive allosteric modulator activity for GABA which is an inhibitory neurotransmitter, DS1 increases the tonic current in thalamus area of the brain. DS2 is a potent δ-selective agoinst found to have selective α4/6β3δ positive allosteric modulator activity. Recently, in the year 2021 Frolund et al. reported a series of DS2 analogues in order to find potent δ-selective allosteric modulators. Inspired from the GABA agonist DS1 and DS2, an attempt was made to design and synthesized novel imidazo[1,2-a]pyridine-3-carboxamide derivatives. It was proposed that the structural determinants of DS1 and DS2 are modified by introducing functionalization on C-5 position by various alkyl and aryl substitution. At C-2 position instead of thiophene, methyl thiophenol has been introduced. N-methoxy amide group were introduced in order to observe the effect of substitution at C-3 position, where R3 could be H, alkyl or benzyl to achieve bioisosteric replacement. Direct C-5 activation in the case of imidazo[1,2-a]pyridine itself is a challenging task. Metal catalysed C-5 activation is much more troublesome therefore; this position has been less explored. In order to find the significance of C-5 substituted analogues of imidazo[1,2-a]pyridine-3-carboxamide this work has been designed. The substitution at C-5 position may affect the δ selectivity which is required to develop a molecule for targeting CNS related diseases. (J. Med. Chem. 2021, 64, 4730).



DS1 (GABA positive allosteric modulator)



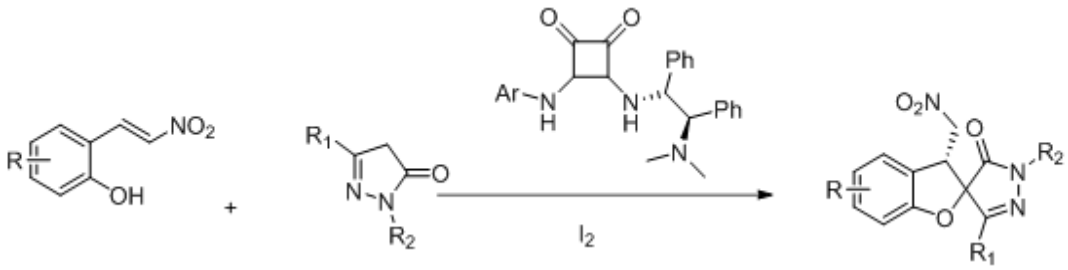
DS2 (GABA positive allosteric modulator)



Designed analogues

Coupled organocatalysis Green synthesis of 2-(azol-1-yl) indoles

The aerobic oxidative cross-coupling of indoles with azoles driven by flavin-iodine-coupled organocatalysis has been developed for the green synthesis of 2-(azol-1-yl) indoles. The coupled organocatalytic system enabled the one-pot three-component synthesis of 2-azolyl-3-thioindoles from indoles, azoles, and thiols in an atom-economical manner by utilizing molecular oxygen as the only sacrificial reagent. In this article development of a simple, convenient, transition metal-free (molecular iodine) catalysed one pot synthesis of 3,5-disubstituted-1,2,4-triazoles. The reaction mechanism involves an initial intermolecular nucleophilic addition (facilitated by I_2) followed by intramolecular nucleophilic cyclisation. It was also demonstrated that 1,1-diaminoazines can act as effective organocatalysts for the formation of phosphorus-carbon bond between biphenylphosphine oxide and an activated alkene (Michael acceptor). These catalysts provide the P-C adducts at a faster rate and with relatively better yields in comparison to the organocatalysts employed earlier.3 Now, our approach is to utilize I2 and 1,1-



diaminoazine in dual catalysis for the formation of heterocycles. (Chem. Comm. 2021, 57, 11717)

Identification of Cryptic Binding Site Using MixMd with standard and Accelerated Molecular Dynamics

Finding and optimizing ligand molecules for a specific binding site is a very efficient method of drug discovery. To do so, it is critical to identify the binding site and comprehend its nature. However, due to the dynamic nature of the protein, which results in numerous conformational states of the binding site, it cannot be easy. When there is a large movement of structures at the binding site, complications arise. Techniques for predicting the binding site based on cosolvent-molecular dynamics have been developed. These strategies take into account the flexibility as well as the effect of the surrounding environment. Mixed Solvent MD (MixMD), SILCS, MDMix, and other approaches fall under this category. The mixed MD approach involved simulating protein in water with probes and detecting the protein surface with the highest probe occupancy. Organic solvents such as isopropanol (IPA), acetonitrile (ACN), pyrimidine (PYR), and others are commonly used as probes. Binding site identification for cryptic sites is a little more difficult. "Cryptic sites are binding sites that are closed in the apostate and open to bind ligands by a structural change." The rearrangement can be as minor as a sidechain rotation or as significant as domain movement." The authors used the MixMD with standard MD and accelerated MD protocol to map the cryptic binding site on the 12 proteins in the current study. The proteins in this list were derived from the Cryptosite dataset. They used five distinct probes: IPA, PYR, ACN, and a set of methylammonium (MAI) + acetate (ACT) ions at the same time. Unbound protein states were employed to test MixMD's competence to introduce conformational changes and map the cryptic site. Using AmberTools and Amber18, they investigated the 12 protein system. This simulation makes use of TIP3P water and the FF14SB forcefield. 12 proteins that are under study were ricin A-chain, adipocyte lipid-binding protein (ALBP), androgen receptor (AR) (ligand-binding domain), secretase (BACE-1), guanylate kinase (kinase domain), lactamase, TIE-2 (kinase domain), protein tyrosine phosphatase 1B (PTP1B, allosteric site), hepatocyte growth factor receptor (c-Met, kinase domain), UDP-N-acetylglucosamine-pyrophosphorylase (UAP1), arylalkylamine N-acetyltransferase (AANAT), and Hsp90. MixMD successfully mapped the system with a wide range of movement, according to the results. For ricin, ALBP, AR, BACE-1, HSP90, Gluanylate kinase, and TIE-2, they were able to identify the binding site and detect suitable conformational sampling.

In the case of BACE-1, where the flaps can close on the binding site, the study was able to facilitate loop movement. Guanylate kinase demonstrated GMP-binding domain mobility, allowing binding site mapping. Furthermore, for guanylate kinase, they utilize charged probes to map the more exposed ATP (ACT, MAI). Although MixMD failed in some cases because whole helices movement was required to open the pocket in those structures. MixMD is thought to have failed due to a short timescale (100ns); another possibility is that the probes were chosen improperly. In conclusion, they stated that there was no consistent probe that mapped well across all of the systems, implying that a variety of probes should be used with MixMD unless first-hand knowledge of the chemical requirements of the desired site is available. (J. Chem. Inf. Model. 2021, 61, 1287).

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