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2,5-Diazabicyclo[2.2.1]heptane in Medicinal Chemistry: A Treasure Trove of Therapeutic Opportunities

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Abstract

2,5-Diazabicyclo[2.2.1]heptane (2,5-DBH) has emerged as a valuable scaffold in medicinal chemistry owing to its conformational rigidity and favorable three-dimensional architecture. In recent years, 2,5-DBH has been increasingly incorporated into biologically active molecules, functioning as a core unit or structural modulator to improve target engagement and pharmacological profiles. Despite growing interest and scattered reports describing its synthesis and biological evaluation, a unified and systematic assessment of this framework has been lacking. This review critically summarizes recent advances in the synthesis of 2,5-DBH and its derivatives, with particular emphasis on efficient construction strategies, functionalization patterns, and derivatization approaches developed over the past decade. In parallel, the biological applications of 2,5-DBH-based compounds are comprehensively discussed across major therapeutic areas, including oncology, neurological disorders, and antimicrobial research. By integrating synthetic progress with biological insights, this review delineates current trends, identifies key structure–activity relationships, and highlights existing challenges and opportunities. Collectively, this work aims to guide future scaffold design and stimulate further exploration of 2,5-DBH as a versatile platform in drug discovery.

Keywords – Anticancer, antimicrobial, bridge piperazine, conformationally restricted, diazabicycloheptane, piperazine analogs, Saturated *N*-heterocycles, 2,5-DBH.

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1. Introduction

Heterocyclic compounds constitute a central class of structures in modern chemical and pharmaceutical research, providing a broad platform for structural diversification and functional modulation of small molecules. A substantial proportion of commercially available drugs incorporates heterocyclic motifs as key components of their molecular frameworks, highlighting their importance in therapeutic development.[1–3] Among the wide range of heterocycles that differ in size, shape, and complexity, nitrogen-containing heterocycles are particularly prominent. Their structural features and biological relevance have driven sustained interest and the development of efficient synthetic methods.[4–6] In 2014, Vitaku *et al*. analyzed U.S. FDA-approved small-molecule drugs up to 2012 and reported that 59% of the approved drugs contained at least one nitrogen heterocycle, establishing these motifs as privileged structures in medicinal chemistry.[7] Building upon this, Marshall *et al.*, extending the analysis through 2023, revealed a substantial increase, with 82% of approved drugs incorporating nitrogen heterocycles and a higher average number of such units per molecule.[8] These findings highlight the growing role of nitrogen heterocycles in drug development.

Within the class of nitrogen-containing heterocycles, saturated nitrogen heterocycles have gained increasing importance in biologically active molecules and play a key role in drug design due to their diverse biological activities and favorable pharmacological properties.[9–11] Among these, piperazine and its analogs represent prominent hetero-aliphatic rings that are widely employed in medicinal chemistry. They have proven particularly valuable as core scaffolds, linkers, and terminal groups in drug discovery.[12,13] An analysis of FDA-approved drugs by Taylor *et al.* revealed that, as of 2014, piperazine ranked as the fourth most prevalent ring scaffold, underscoring its privileged status across multiple therapeutic areas.[3] Various piperazine analogs—such as homopiperazine, spiro-piperidine, and bicyclic piperazine—offer structural diversity while retaining key physicochemical properties, making them valuable tools in drug design and development. Notably, conformationally restricted piperazines have emerged as a particularly significant subclass.[14,15]

The concept of "conformational restriction" has gained prominence in contemporary chemical literature, referring to molecular frameworks designed to limit intramolecular flexibility, thereby enhancing selectivity, metabolic stability, and receptor binding

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affinity. Fused, bridged, and spirocyclic scaffolds contribute significantly to the rigidity of hetero-aliphatic rings by imposing structural constraints. Piperazine analogs featuring these scaffolds are commonly referred to as conformationally restricted diamines (CRDAs) and provide precisely defined molecular frameworks, ensuring that nitrogen atoms are maintained at specific distances and orientations. This rigidity makes CRDAs particularly valuable in enhancing the specificity, stability, and overall efficacy of pharmaceutical compounds.[16,17]

Bridged bicyclic analogs of piperazine predominantly exist in two structural forms (**Fig. 1.**): the 2,5-bridged and the 2,6-bridged piperazine analogs. In the 2,5-bridged variants, the piperazine ring is conformationally constrained into a distorted boat geometry,[18–20] whereas in the 2,6-bridged analogs, the bicyclic framework locks the piperazine ring into a chair conformation.[21,22] These distinct conformational constraints impart unique structural and functional properties, enhancing their utility in medicinal chemistry for fine-tuning drug design, receptor binding, and biological activity.[23,24]

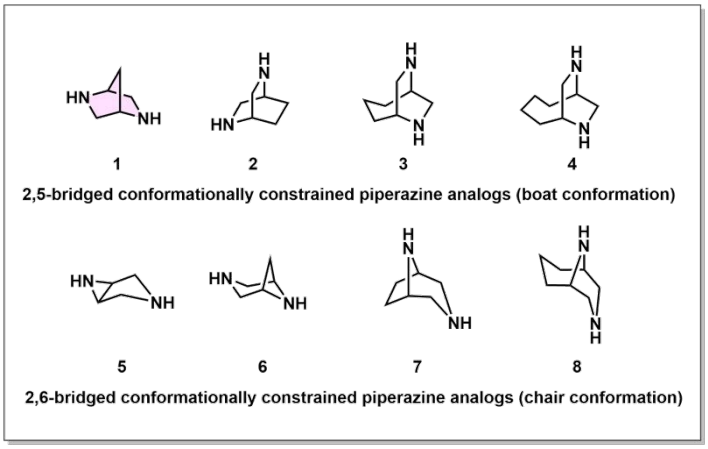

Fig. 1. Bridged conformationally constrained piperazine analogs.

Among the bridged piperazine analogs, 2,5-diazabicyclo[2.2.1]heptane (2,5-DBH) has gained increasing attention as a compact and rigid scaffold with distinctive structural features. As a member of the diazabicycloheptane family, 2,5-DBH represents a conformationally constrained counterpart of piperazine and has been incorporated into a variety of bioactive molecules. Compounds bearing the 2,5-DBH motif have been reported to exhibit activity across a broad range of therapeutic indications, including oncology, infectious diseases, inflammation, and disorders of the central nervous system.[25] Notably, this scaffold has also been identified among the frequently utilized ring systems in U.S. clinical trials, highlighting its translational relevance. [26]

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In recent decades, exploration of 2,5-DBH has been emphasized due to its diverse therapeutic potential. Till now, the moiety has been explored under several disease conditions, including antitumor, antimicrobial, anti-inflammatory, antipsychotic, anti-Alzheimer's, and cardiovascular protective effects. This review focuses on the synthetic strategies employed to construct compounds featuring the 2,5-DBH scaffold, highlighting recent advancements, key methodologies, and structure-activity relationships. Furthermore, it delves into the biological evaluation of these derivatives, highlighting their therapeutic potential and exploring their effectiveness across diverse biological systems. The aim is to provide an in-depth understanding of both the synthetic approaches and the pharmacological applications of these compounds.

2. Structural and Physicochemical Features of the 2,5-DBH Scaffold

2,5-DBH is a rigid counterpart of piperazine with a distorted boat conformation that exists in two enantiomeric forms (*1S,4S*)-2,5-diazabicyclo[2.2.1]heptane ((*1S,4S*)-2,5-DBH) (**1**) and (*1R,4R*)-2,5-diazabicyclo[2.2.1]heptane ((*1R,4R*)-2,5-DBH) (**9**) (**Fig. 2**).[25] Britvin *et al*. synthesized and crystallized the (*1S,4S*)-2,5-diazabicyclo[2.2.1]heptane and reported its crystal structure in 2017.[27]

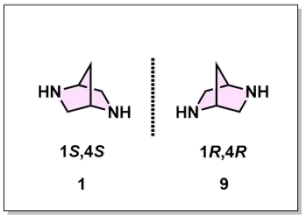

Fig. 2. Mirror image of 2,5-DBH

Owing to its rigid bicyclic diamine framework bearing two secondary amine functionalities at the 2- and 5-positions, 2,5-DBH exhibits a polar surface area of 24.1 Å² and a logP value of −0.6, features that enable a wide range of inter- and intramolecular interactions. In its diprotonated dihydrobromide form, single-crystal X-ray analysis reveals two independent cage units interconnected through an extensive three-dimensional N–H···Br hydrogen-bonding network involving four bromide counterions, highlighting its strong intermolecular hydrogen-bonding capacity. Additionally, the availability of nitrogen lone pairs facilitates coordination with metal ions, as demonstrated by reported copper(II) complexes of substituted 2,5-DBH derivatives.[27,28] The bridged, piperazine-like architecture, characterized by a short

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N···N separation of approximately 2.87–2.91 Å, further promotes intramolecular dipole–dipole and electrostatic interactions.[29]

3. Synthesis of 2,5-diazabicyclo[2.2.1]heptane

3.1 Synthesis of 2,5-diazabicyclo[2.2.1]heptane from 4-hydroxy-L-proline

Due to its versatility in producing both 1*S*,4*S*-2,5-DBH (**1**) and 1*R*,4*R*-2,5-DBH (**9**) isomers with high yields, 4-hydroxy-*L*-proline (**10**) has been widely adopted by researchers as the starting material for synthesizing 2,5-DBH. The stereochemistry of the intermediates (*2S,4R*) (**14**) and (*2S,4R*) (**32**) decides whether the product will be in the (1*S*,4*S*) or (*1R,4R*) configuration (**Fig. 3**).[30,31] The cyclization via intermolecular nucleophilic substitution reactions of (*2S,4R*) (**14**) at the second position attacks the activated C–O functionality at C-4, closing the five-membered pyrrolidine ring to form a rigid fused ring system (1*S*,4*S*)-2,5-DBH (**1**), while (*1R,4R*)-2,5-DBH (**9**) was synthesized via cyclization of (*2S,4R*) (**32**) via reversible epimerization at C-2 under basic conditions, producing a transient (*2R*) epimer. This epimer, now correctly oriented for ring closure, undergoes an intramolecular aminolysis of the ester group to form a bridged lactam intermediate. This lactam then undergoes deprotonation and further anchimeric assistance to afford the desired bicyclic scaffold. However, the preparation of the (1*R*,4*R*)-2,5-DBH isomer involves additional steps (**Scheme 5**)[31] to establish the correct stereochemistry, resulting in a significantly longer synthetic route compared to the (1*S*,4*S*)-2,5-DBH isomer (**Scheme 2**).

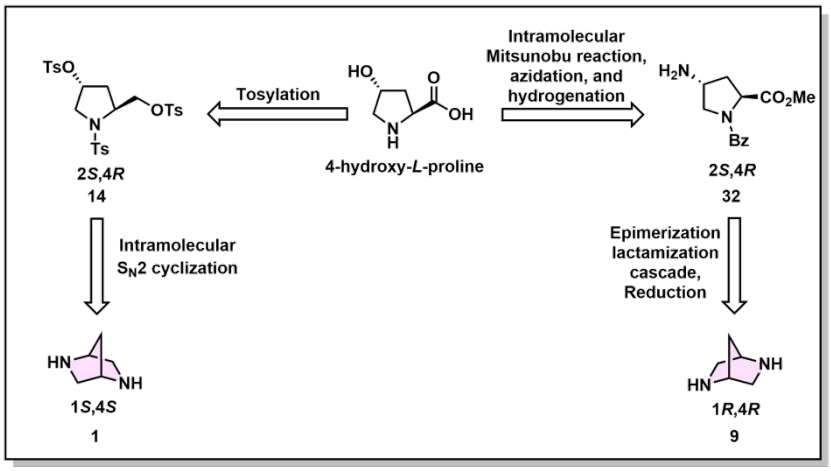

Fig. 3. Different mechanisms involved in the synthesis of **compound (1)** and **compound (9)**

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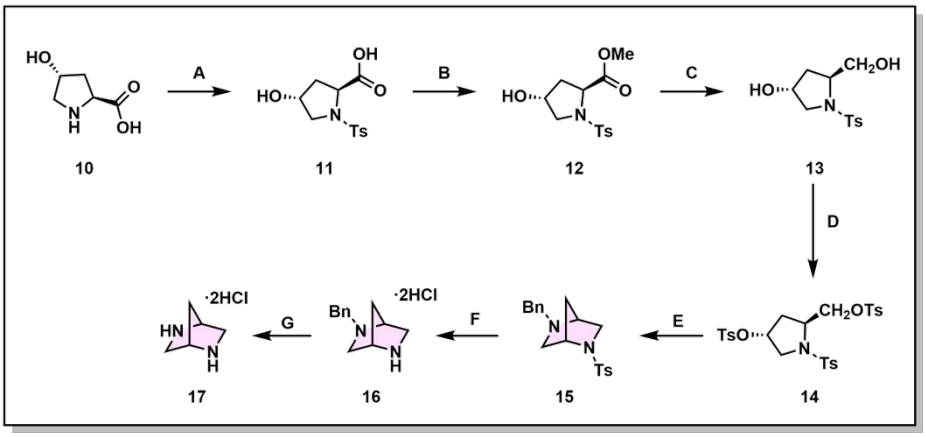
The synthesis of 2,5-DBH was initially documented by Portoghese *et al*. in 1966 (**Scheme 1**), employing a novel synthetic route. The route began with *N*-terminal protection of trans-4-hydroxy-*L*-proline (**10**) via tosylation, affording compound (**11**). Subsequent esterification furnished the methyl ester derivative (**12**), which was then reduced to yield *N*-tosyl hydroxy-*L*-prolinol (**13**). Further tosylation in pyridine generated the corresponding tritosylate (**14**), which underwent intramolecular S_N2 ring closure to provide the benzyl-substituted 2,5-DBH intermediate (**15**). Refluxing this compound afforded the dihydrochloride salt (**16**). Finally, catalytic hydrogenolysis proceeded efficiently to deliver the parent bicyclic diamine as its dihydrochloride salt (**17**) in excellent yield.[30]



Scheme 1. A) TsCl, 2-N NaOH solution in ether, rt, 5 h, 96%; B) CH_2N_2 ether solution, MeOH, 91%; C) $LiBH_4$, THF 0 ºC to rt, 7 h 86%; D) TsCl, Pyridine, 87%; E) $BnNH_2$, toluene, reflux, 50 h 86%; F) HCl:glacial acetic acid:water, red phosphorus, reflux, 3.5 h then rt overnight, 85%

Melgar-Fernández *et al*. synthesized chiral derivatives of (1*S*,4*S*)-2,5-DBH under microwave irradiation (**Scheme 2**). The synthesis commenced with the reaction between (S)-trans-4-hydroxyproline (10) and p-toluenesulfonyl chloride in an aqueous sodium carbonate solution. Under microwave conditions, the reaction was completed within 30 minutes, producing (**14**) a high yield. The product was then reduced using diborane, followed by tosylation to yield the tritosylate derivative (**15**). The tritosylate derivative was subsequently cyclized with selected primary amines under microwave irradiation, which afforded the desired 5-benzyl-2-tosyl-2,5-DBH (**18**) in 30 minutes. Finally, hydrogenolysis of (**18**) using palladium on charcoal facilitated debenzylation, yielding the parent compound, hydrobromide salt of (1*S*,4*S*)-2,5-DBH (**19**)[32]

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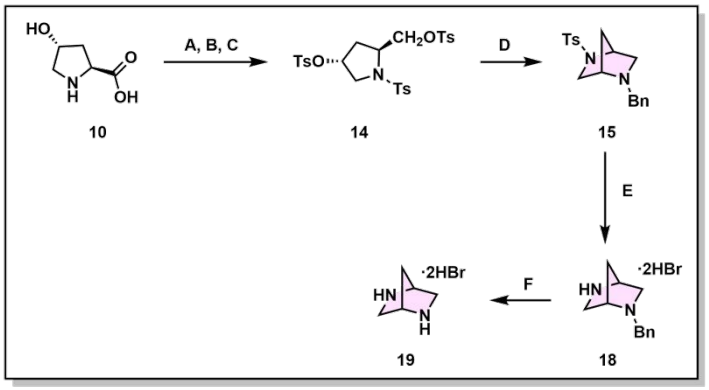
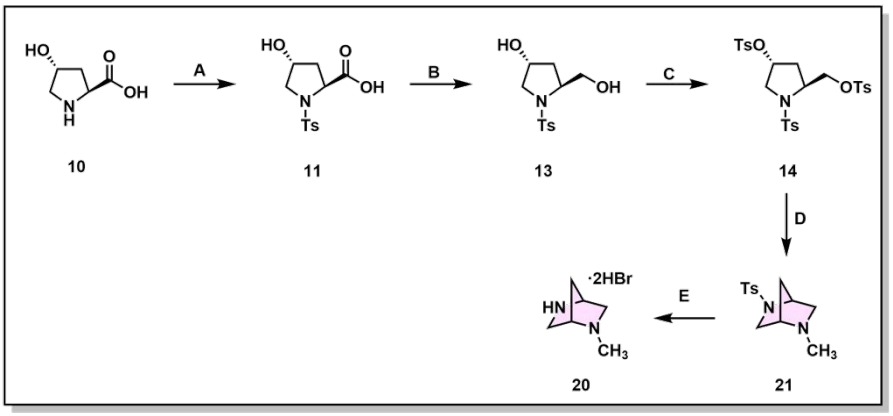


Scheme 2. A) TsCl, Na_2CO_3, H_2O, MW 100 W at 100 °C, 30 min, 95%; B) $NaBH_4/BF_3{\cdot}Et_2O$, THF, reflux, 15 h, 85%; C) TsCl, Pyridine 20 h, 95%; D) $BnNH_2$, toluene, reflux, 2 h, 93%; E) HBr, MW 100 W at 100 °C, 30 min, 98%; F) H_2, 10% Pd/C, $MeOH/H_2O$, 1 h, 94%.

In the context of designing the side chains of danofloxacin, Braish *et al*. developed a scalable commercial route on a 100 kg scale (**Scheme 3**). The process was initiated with the protection of the nitrogen atom in *L*-4-hydroxyproline (**10**) using *p*-toluenesulfonyl chloride to afford intermediate (**11**). This intermediate was then reduced, forming (**13**). Subsequently, the tritosylate derivative (**14**) was produced using p-toluenesulfonyl chloride. This tritosylate derivative was then cyclized with methylamine, yielding the intermediate (**20**). Finally, the tosyl group was removed from the *N*-position of (**20**), resulting in the final compound (**21**).[33]



Scheme 3. A) TsCl, Na_2CO_3, water, quantitative yield; B) $NaBH_4$, THF, BF_3, Etherate, 85%; C) TsCl, TEA, 90%; D) CH_3NH_2, MeOH, 86%; E) 30% HBr, AcOH, 88%.

The interest towards the medicinal chemistry of 2,5-DBH led Beinat *et al*. to develop a new, efficient synthetic route for producing (1*S*,4*S*)-2,5-DBH (**1**) on a gram scale (**Scheme 4**). The procedure encompassed the methyl esterification of *L*-4-

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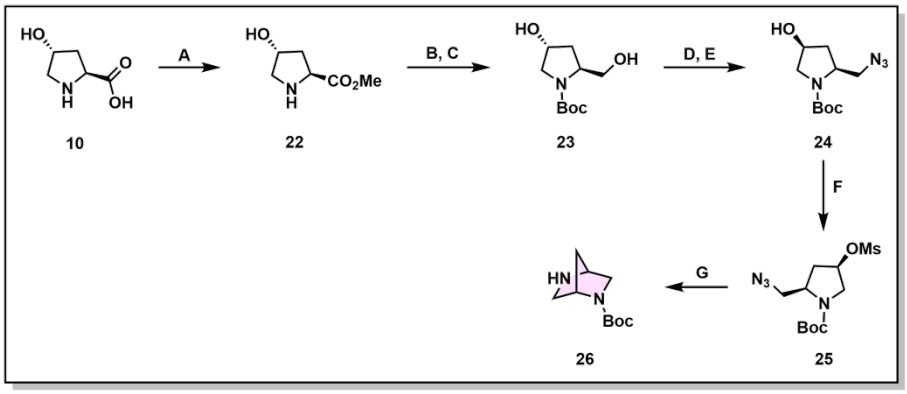
hydroxyproline (**10**), which afforded (**22**) as a hydrochloride salt. In the next step, the secondary amine was protected with a tert-butyloxycarbonyl (Boc) group, and the methyl ester was chemoselectively reduced to the diol (**23**). Selective tosylation of the primary hydroxyl group, followed by azide displacement, resulted in (**24**). The secondary hydroxyl group was activated by treatment with mesyl chloride to give (**25**). Finally, Staudinger reduction of the azide triggered spontaneous transannular cyclization, with the liberated primary amino group displacing the mesyl group and furnishing the mono-protected (1*S*,4*S*)-2,5-DBH building block (**26**).[34]



Scheme 4. A) MeOH, HCl, 0 °C to rt 17 h, 100%; B) $(Boc)_2O$, TEA, DCM, 0 °C to rt, 17 h, 97%; C) $LiBH_4$, THF, 0 °C to rt, 24 h, 94% D) TsCl, Pyridine, DCM, 40 °C, 8 h, 69%; E) $TMSN_3$, TBAF, THF, 70 °C, 18 h, 79%; F) MsCl, TEA, DCM, 0 °C, 30 min., 95%; G) PPh_3, THF, H_2O, rt, 18 h 71%;

Cui *et al*. reported an epimerization–lactamization strategy for synthesizing (1*R*,4*R*)-2,5-DBH (**2**) (**Scheme 5**). The first phase of the synthesis involved producing (2*S*,4*R*)-1-benzoyl-4-amino-prolinemethylester (**32**), starting with *trans*-4-hydroxy-*L*-proline (**10**). The *N*-position of this compound was protected by the dropwise addition of benzoyl chloride, yielding another intermediate (**27**). This intermediate was further reacted with Diethyl azodicarboxylate (DEAD) and triphenylphosphine to produce the next compound (**28**). The reaction mixture was then stirred at 40 ºC for 5 h with sodium azide, resulting in the methyl ester derivative (**29**). The alcohol group was subsequently reacted with mesyl chloride under inert and basic conditions to obtain another intermediate (**30**). Under anhydrous conditions, this compound was stirred at 70 °C for 6 h with sodium azide, resulting in the formation of the next intermediate (**31**). Finally, (2*S*,4*R*)-1-benzoyl-4-amino-prolinemethylester (**32**) was obtained by stirring the compound under hydrogen (1 atm) in the presence of 10% Pd/C. The subsequent phase of the procedure employed (2*S*,4*R*)-1-benzoyl-4-amino-prolinemethylester (**32**)

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as the starting material (**Fig. 4**). This ester was treated with potassium bis(trimethylsilyl)amide (KHMDS) in an anhydrous THF solution under a nitrogen atmosphere at rt, which led to the intramolecular aminolysis of the (2*R*)-epimer, forming a cyclic lactam intermediate (**33**). The intermediate was then reduced using $LiAlH_4$, after which the free amino group was protected with Boc_2O (**34**). In the final step, the compound was stirred under hydrogen gas in the presence of 10% Pd/C, ultimately yielding the desired product, mono-protected (1*R*,4*R*)-2,5-DBH building block (**35**).[31]

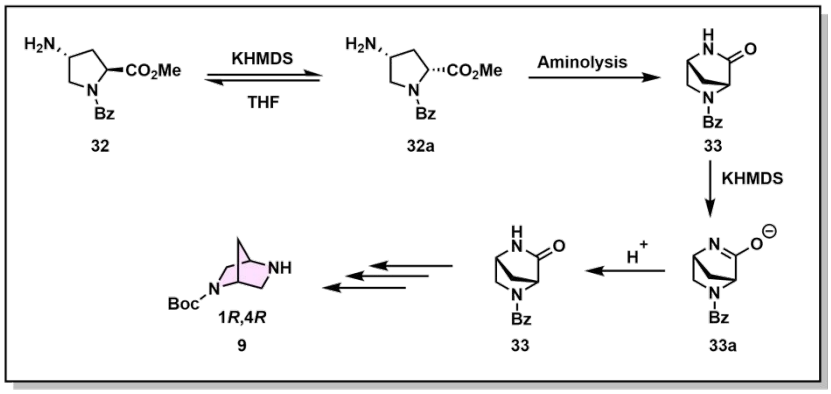
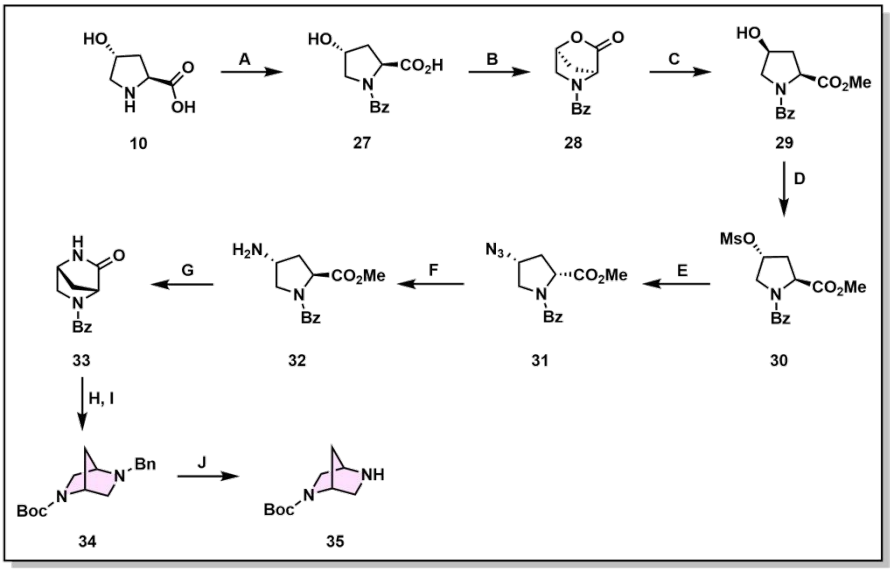


Fig. 4. Mechanism of the epimerization–lactamization cascade



Scheme 5. A) BzCl, NaOH, H_2O, 0 ºC to rt, 20 h, 99%; B) DEAD, PPh_3, THF, rt, 87%; C) NaN_3, MeOH, 40 ºC, 5 h, 90%; D) MsCl, TEA, DCM, 0 ºC, 98%; E) NaN_3, DMF, 70 ºC, 6 h, 97%; F) H_2, 10% Pd/C, MeOH, rt, 89%; G) KHMDS, THF, r.t., 15 min, 96%; H) $LiAlH_4$, THF, reflux, 1h, 71%; I) $(Boc)_2O$, 2N NaOH, 71%; J) H_2, 10% Pd/C, MeOH, 81%.

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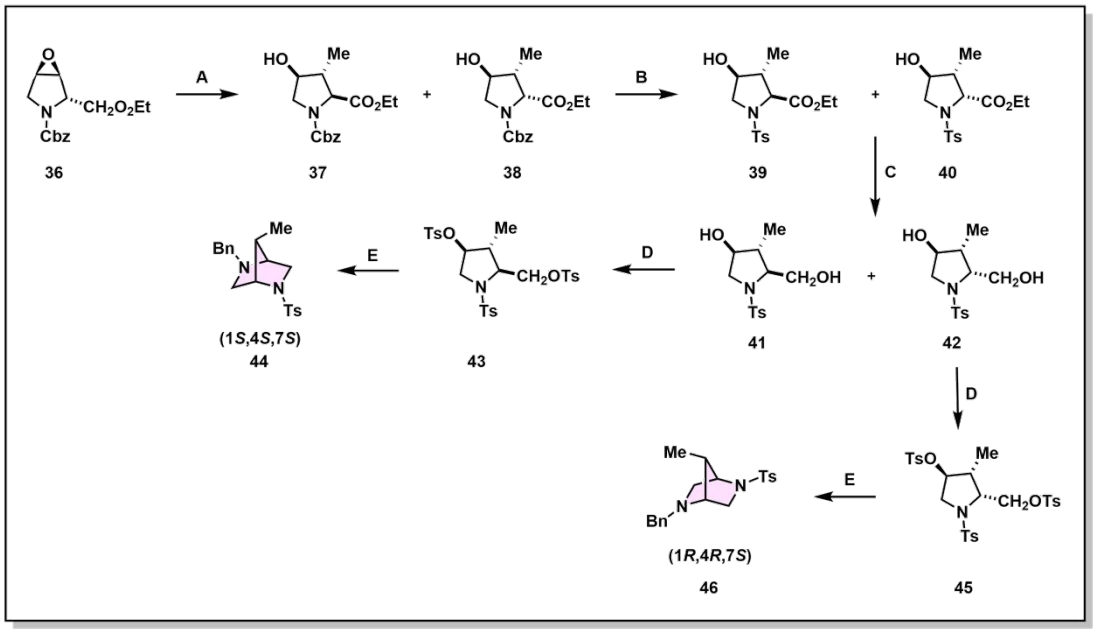
3.2 Synthesis of 2,5-Diazabicyclo[2.2.1]heptane from other starting materials

Despite using 4-hydroxy-*L*-proline, some researchers utilized different starting materials for the synthesis of both isomers of 2,5-DBH.

Remuzon *et al*. published the synthesis of (1*S*, 4*S*, 7*S*)- (**44**) and (1*R*, 4*R*, 7*S*)-2-(4-tolylsulfonyl)-5-phenylmethyl-7-methyl-2,5-diazabicyclo[2.2.1]heptanes (**46**) from 3,4-epoxy-*D*-proline (**36**) (**Scheme 6**). Initial attempts to introduce a methyl group involved opening the epoxide ring, resulting in a mixture of compounds, including diastereoisomers of (**37**) and (**38**). This mixture was then subjected to catalytic hydrogenation, followed by tosylation, which produced a second set of diastereoisomers (**39**) and (**40**). Further reduction of these diastereoisomers yielded diols that constituted a third set of diastereoisomers (**41**) and (**42**), which were separated via chromatography. Subsequent reactions were carried out on these compounds separately. The diols were further tosylated to yield the corresponding tritosylates: (2*S*,3*R*,4*S*) (**43**) and (2*R*,3*R*,4*S*) intermediate (**45**). Upon reaction with benzylamine in refluxing xylene, the (**43**) afforded the (1*S*,4*S*,7*S*)-2,5-diazabicyclo[2.2.1]heptane (**44**) derivative with a yield of 49%, while the (**45**) produced the (1*R*,4*R*,7*S*)-2,5-diazabicyclo[2.2.1]heptane (**46**) derivative with a yield of 86%.[35]



Scheme 6. Synthesis of (1*S*, 4*S*, 7*S*) and (1*R*, 4*R*, 7*S*) methyl derivatives of 2,5-DBH from 3,4-epoxy-*D*-proline. Reagents and conditions: A) Me_2CuLi, Et_2O, -10 ºC, 1 h, 81%; B) H_2, PD/C, MeOH, rt, 1.5 h, 71%; C) TsCl, pyridine, 5 ºC, 24 h; D) $LiBH_4$, THF 0 ºC to rt, 4 h 94-96%; E) $BnNH_2$, xylene, reflux, 24 h, 1*S*, 4*S*, 7*S* 49% and 1*R*, 4*R*, 7*S* 86%.

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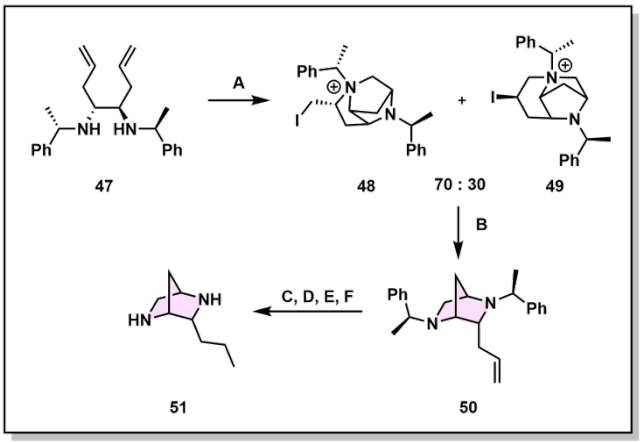
Fiorelli *et al*. reported a stereoselective synthesis of DBH, enabled by iodine-mediated cyclization (**Scheme 7**). The strategy involves the cyclization of unsaturated amines upon treatment with either iodine or *N*-iodosuccinimide. A key step in this transformation was the cyclization of (4*R*,5*R*)-4,5-diamino-*N,N*-bis[(1*S*)-1-phenylethyl]-1,7-octadiene (**47**) in the presence of iodine. This reaction yields two bridged tricyclic ammonium salt frameworks: the major isomer (**48**) and a minor isomeric salt (**49**). The structure of the predominant product (**48**) was conclusively confirmed through X-ray diffraction analysis. Subsequent treatment of both ammonium salts with organometallic reagents facilitated the formation of the 2,5-DBH core (**50**) via an iodine/metal exchange followed by *β*-cleavage. Final hydrogenolysis of the benzylic *N*-substituents in compound **50**, along with concurrent hydrogenation of the carbon–carbon double bond, efficiently yielded the desired bridged piperazine (**51**).[36]



Scheme 7. Synthesis of 3-alkyl substituted-2,5-DBH facilitated by iodine. Reagents and conditions: A) I_2 2 eq, $NaHCO_3$, DCM/water; B) *n*-BuLi 2.5 eq, THF, 0 ºC, 1 h, 69%; C) HCO_2NH_4, 5% Pd/C, EtOH, reflux; D) HCl, EtOH, 76%; E) crystallisation; F) NaOH, DCM, 62%

Within the same research group, Alvaro *et al*. delved deeper into the potential of this novel synthetic approach to the bicyclic skeleton, with a particular emphasis on the role of chain substituents at various locations within the precursor 4,5-diamino-1,7-octadiene (**52**) (**Scheme 8**). Their study demonstrated that the substituent positioned at the alkene terminus does not undergo the anticipated subsequent iodo-cyclization to yield the corresponding tricyclic ammonium salts. Instead, the presence of this substituent inhibits the second iodocyclization step, likely due to steric effects, thereby

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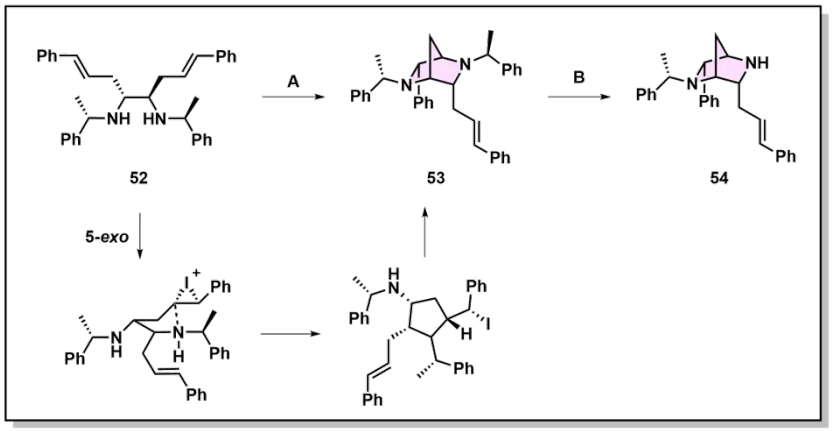
enabling the direct one-step formation of 3,6-*cis*-disubstituted bridged piperazines (**53**). The mechanism entails a 5-*exo*-iodo-cyclization step, leading to the formation of the substituted pyrrolidine through the transition state. This is subsequently followed by a swift intramolecular substitution, where the secondary amine attacks the highly reactive iodide, culminating in the formation of the bridged piperazine (**54**).[37]



Scheme 8. Synthesis of 3-substituted-2,5-DBH from 4,5-diamino-1,7-octadiene. Reagents and conditions: A) I_2, $NaHCO_3$, DCM/water, rt, 58-61%; B) HCO_2NH_4, Pd/C, EtOH, reflux, 3h, 77%.

The application of diamino acids as branching units in peptides and as versatile building blocks in drug discovery is well established. In this context, Ivon *et al*. reported the synthesis of orthogonally protected *α*,*β*-diamino acid derivatives incorporating the conformationally rigid 2,5-DBH scaffold (**Scheme 9**). The synthetic strategy was based on a tandem Strecker reaction–intramolecular nucleophilic cyclization (STRINC), enabling the formation of tert-butyl (1*S*,4*S*)-5-benzyl-4-cyano-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**56**). This key intermediate was generated through the reaction of tert-butyl (*S*)-2-(bromomethyl)-4-oxopyrrolidine-1-carboxylate (**55**) with benzylamine and acetone cyanohydrin. Acidic hydrolysis of compound (**56)** yielded the corresponding dihydrochloride salt of the amino acid (**57**). Subsequent debenzylation using hydrogenation over Pd/C afforded the fully deprotected amino acid, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-1-carboxylic acid (**58**).[38]

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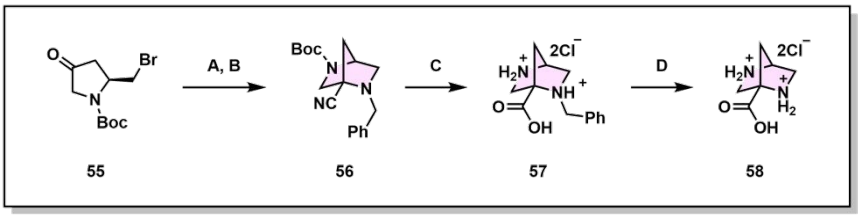

Scheme 9. Synthesis of conformationally rigid bicyclic *α*, *β*-diamino acid derivatives. Reagents and conditions: A) $BnNH_2$, acetone cyanohydrin, MeOH, rt, 20 min; B) MeOH, reflux, 4 h, 33%; C) 6-M aq. HCl, reflux, 2 weeks, 83%; D) 10% Pd/C in water was hydrogenated in an autoclave under 40 atm of H_2 at 70 °C for 2 days, 90%.

4. Synthesis and Biological Profile of Various 2,5-Diazabicyclo[2.2.1]heptane Derivatives

4.1 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Mono-aza-heterocycles.

Several saturated and unsaturated heterocycles containing a single nitrogen atom, known as mono-aza-heterocycles, such as pyridine, piperidine, indole, quinoline, pyrrole, and piperidine, are widely recognized as valuable scaffolds in medicinal chemistry.[39–41] Many research groups have explored these scaffolds conjugated with 2,5-DBH to develop compounds with promising biological activity.

Bruton's Tyrosine Kinase (BTK) is part of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family and is predominantly found in hematopoietic cells, including B-cells, macrophages, monocytes, and mast cells. Small-molecule covalent irreversible BTK inhibitors, such as ibrutinib, specifically target the Cys481 residue within the ATP-binding pocket and are utilized in treating B-cell malignancies.[42–44] In their study, Qiu *et al*. began with a fragment hit and identified a new series of potent, covalent, irreversible BTK inhibitors that interact with the selectivity pocket of the BTK kinase domain's active site. Utilizing X-ray crystallography and a fragment-based drug design (FBDD) strategy, they developed compounds that exhibited cellular potency comparable to ibrutinib and improved selectivity against undesirable off-target kinases like DCTPase. Compound (**64**), featuring a 2,5-DBH framework (**Scheme 10**), displayed significant BTK enzyme activity with an IC_{50} value of 12 nM.[45]

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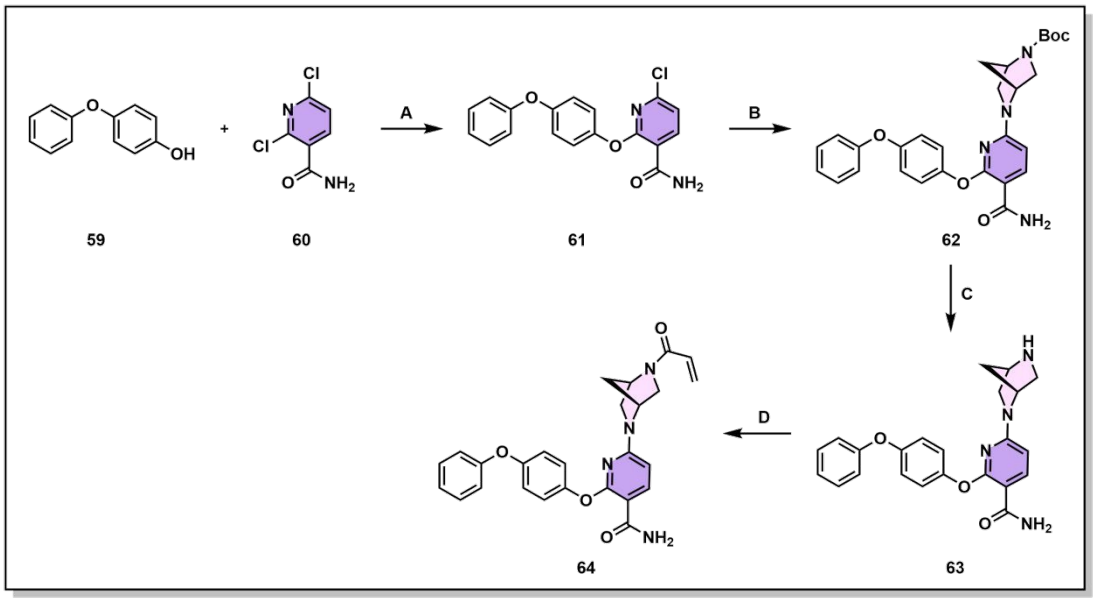

Scheme 10. Synthesis of 4-phenoxy nicotinamide containing 2,5-DBH. Reagents and Conditions: A) Cs_2CO_3, DMF, rt, 2 h 93%; B) *N*-Boc-2,5-DBH, DIPEA, DMF, 80 °C; C) HCl, MeOH, rt, 12 h, quantitative; D) acrylic acid, T3P, DCM, rt, 15 min 40%.

Acquired immunodeficiency syndrome (AIDS), which is brought about by the human immunodeficiency virus (HIV), represents one of the most severe health challenges facing humanity today.[46] Despite the advancements made through highly active antiretroviral therapy (HAART)—a treatment strategy that employs a combination of medications designed to inhibit the actions of HIV-1 protease and reverse transcriptase—significant issues remain.[47] While HAART has been effective in substantially lowering the rates of mortality and morbidity associated with HIV-1, many patients continue to endure lifelong adherence, toxicity, drug interactions, and drug resistance.[48] CCR5, a seven-transmembrane G-protein coupled receptor, is crucial for R5-tropic HIV-1 entry into host cells. This pivotal role has driven the development of novel CCR5 antagonists to combat HIV-1 infections.[49,50] In their research, Hu *et al*. synthesized novel compounds designed to function as CCR5 antagonists. The CCR5 antagonistic properties of these newly synthesized compounds were evaluated through a calcium mobilization assay, which demonstrated that the derivative based on 2,5-DBH (**69, Scheme 11**) exhibited potent CCR5 antagonism, with an IC_{50} value measured at 8.8 nM. CHO cells stably expressing CCR5 and Gα16 were loaded with 2 μmol/L Fluo-4 AM in HBSS (pH 7.4) at 37°C for 45 min. Cells were rinsed, then incubated with 50 μL HBSS containing antagonists (positive control), test compounds,

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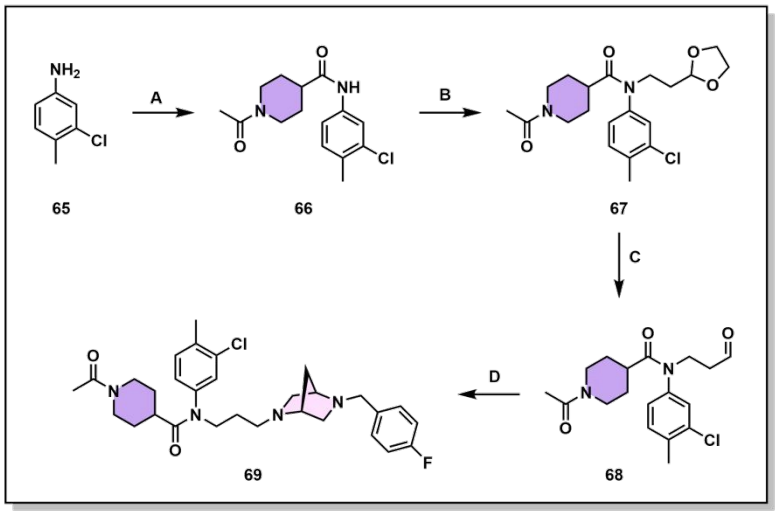
or 1% DMSO (negative control) for 10 min at room temperature. Agonist RANTES (final 3 nmol/L) was added via FlexStation II, and Ca^{2+} changes recorded (excitation 485 nm, emission 525 nm). IC_{50} values were calculated from dose-response curves.[51]



Scheme 11. Synthesis of piperidine linked 2,5-DBH derivative. Reagents and conditions: A) EDC, R_4COOH, DCM, rt, 12 h, 76%; B) 2-(2-bromoethyl)-1,3-dioxolane, NaH, DMF, 80 °C,12 h, 80-90%; C) 1-N HCl, 18 h 70-90%; D) (1*S*,4*S*)-2-(4-fluorobenzyl)-2,5-DBH, $NaBH(OAc)_3$, rt, 6 h, 41%.

Human African trypanosomiasis (HAT), a neglected tropical disease, is caused by the protozoan parasite *Trypanosoma brucei*. Two subspecies are responsible for human infections: *T.b. gambiense*, which causes a chronic form of the disease prevalent in western and central Africa, and *T.b. rhodesiense*, which leads to an acute, rapidly progressing form found primarily in eastern and southern Africa. If left untreated, HAT is uniformly fatal. Lapatinib, a well-established epidermal growth factor receptor (EGFR) inhibitor, has been investigated as a scaffold for developing novel therapeutic agents targeting *T. brucei*, the causative organism of HAT.[52,53] This research resulted in the identification of compound (**70**), which is part of a chemical series typically characterized by poor aqueous solubility. As a follow-up, medicinal chemistry efforts were directed toward enhancing the aqueous solubility and improving the physicochemical properties of this series while ensuring that its anti-trypanosomal effectiveness was preserved (**Fig. 5**).

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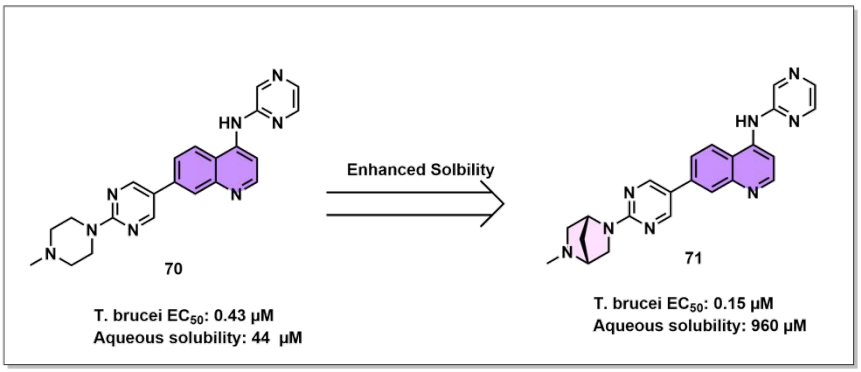
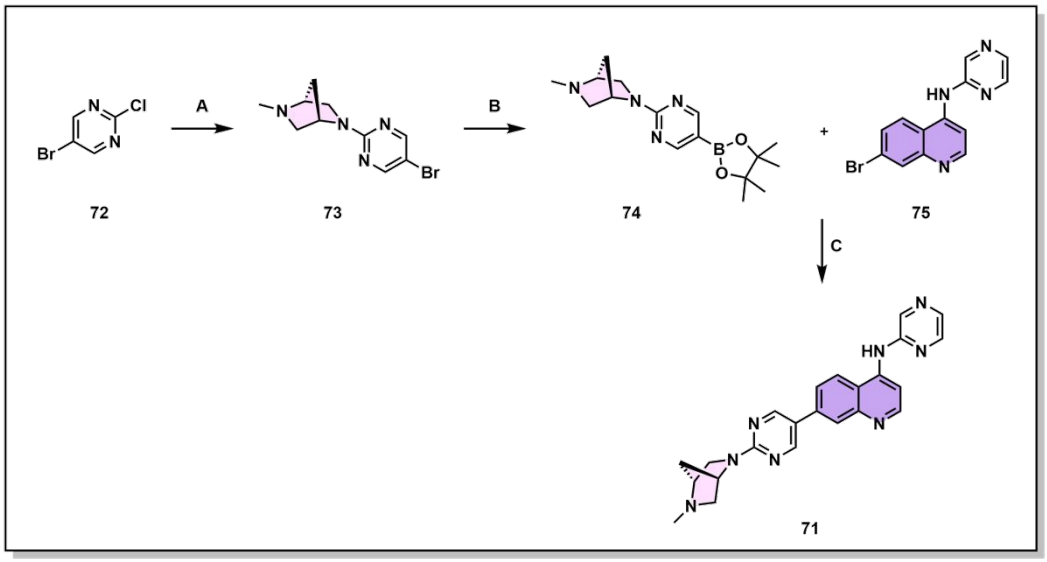


Fig. 5. Aqueous solubility and EC_{50} value of quinoline containing 2,5-DBH

Bachovchin *et. al*. proposed a strategy involved increasing the sp^3 content of the tail group and replacing the piperazine ring with moieties that exhibit greater three-dimensional characteristics. This modification led to the creation of bridged piperazine derivatives, which demonstrated a remarkable 20-fold improvement in aqueous solubility alongside a slight enhancement in potency against *T. brucei*. Additionally, these modifications resulted in improved lipophilic ligand efficiency (LLE) and a four-fold increase in metabolic stability. Further analysis of the Log D values indicated that the incorporation of a one-carbon bridge into the piperazine structure resulted in a decrease in Log D, suggesting an alteration in the compound's hydrophobic properties (**71**) (**Scheme 12**). Notably, this final compound exhibited enhanced aqueous solubility and potent anti-trypanosomal activity, showing an IC_{50} value of 0.15 µM (**Fig. 5**).[54]



Scheme 12. Synthesis of Lapatinib-derived analogues coupled with 2,5-DBH. Reagents and conditions: A) Substituted amines, TEA, EtOH, ambient temperature, 18 h, 72%; B) B_2pin_2, KOAc, $PdCl_2(dppf)\cdot CH_2Cl_2$, dioxane, 145 °C, 1 h, 49%; C) K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$, 3:1 dioxane/water, 130 °C, microwave, 30 min, 21%.

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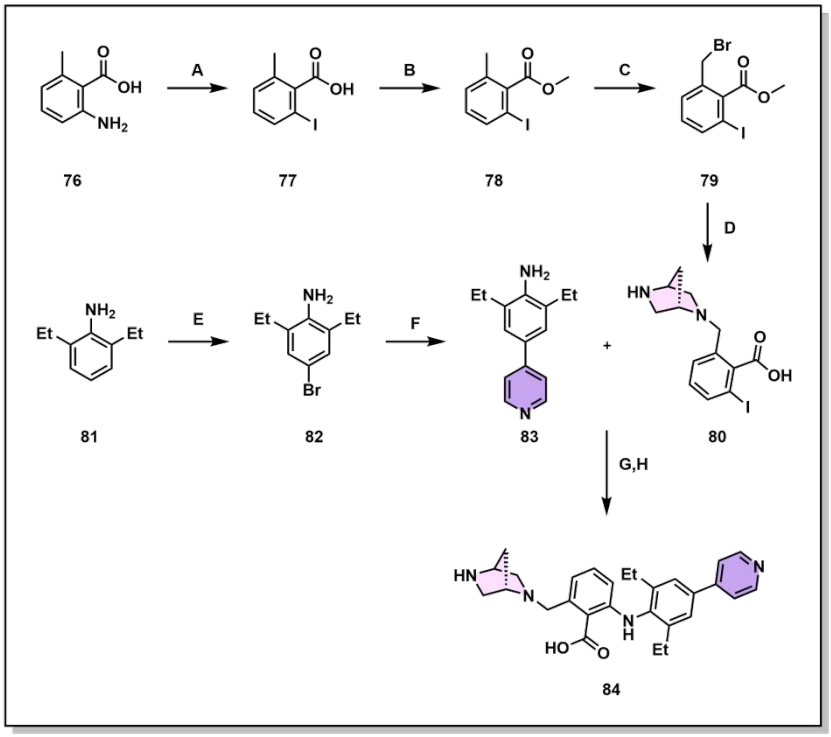
Over the past decade, the field of RNA epigenetics has significantly advanced our understanding of gene regulation, development, and disease mechanisms, with more than 170 distinct RNA modifications identified to date. Among these, N6-methyladenosine (m6A) is the most prevalent and functionally significant modification found in both eukaryotic messenger RNA (mRNA) and non-coding RNA.[55,56] The 2011 discovery of fat mass and obesity-associated protein (FTO), the first RNA demethylase, revealed that m6A modifications can be reversed. This regulation involves proteins that add (writers), remove (erasers), and interpret (readers) m6A. FTO dysregulation can disrupt m6A balance, contributing to diseases like acute myeloid leukemia (AML), melanoma, and breast cancer, making it a promising therapeutic target.[57,58] Xiao *et al*. developed benzoic acid inhibitors of FTO to enhance antileukemia properties. One of the derivatives based on 2,5-DBH (**84**) showed promising activity, exhibiting 37% FTO inhibition at 20 μM. The reaction conditions are provided in (**Scheme 13**).[59]



Scheme 13. Synthesis of benzoic acid-based FTO inhibitor coupled with 2,5-DBH. Reagents and conditions: A) $NaNO_2$, concentrated HCl, KI, H_2O, 0 °C to 90 °C, 3 h; B) $(CH_3O)_2SO_2$, K_2CO_3, DMF, rt, overnight, 43%; C) NBS, BPO, benzene, refluxing, overnight, 67%; D) amine, TEA, DCM, rt, overnight, 51%; E) Br_2, DCM, 0 °C to rt, overnight, 93%; F) Boronic acid or ester, $Pd(PPh_3)_4$, K_3PO_4, toluene/EtOH, 80 °C, 24 h, 75%; G) $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 110 °C, 24−48 h; H) KOH, EtOH/H_2O, 95 °C, overnight; then diluted with 2-M HCl, 60%.

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Chromosomal translocations involving the mixed lineage leukemia 1 (MLL1 or MLL) gene are observed in approximately 5–10% of adult acute leukemias and in nearly 70% of infant acute lymphoblastic leukemia (ALL) cases. In acute myeloid leukemia (AML), MLL rearrangements (MLLr leukemia) are associated with poor prognosis, with a 5-year survival rate of only around 35%. These leukemias often exhibit resistance to standard therapies, underscoring the urgent need for novel therapeutic strategies. The translocations result in the fusion of MLL with more than 80 different partner genes, generating chimeric transcripts that encode oncogenic MLL fusion proteins. A critical driver of MLLr leukemia is the interaction between these fusion proteins and the co-factor menin, which is essential for the aberrant activation of MEIS1 and HOXA genes, thereby promoting leukemogenesis.[60] Targeting the menin-MLL protein interaction is being investigated as a potential treatment. Zhang *et al*. introduced M-1121 (**91**) (**Scheme 14**), a covalent, orally administered inhibitor that effectively induces complete tumor regression. M-1121 binds covalently to Cysteine 329 within the MLL binding pocket of menin, thereby inhibiting the growth of acute leukemia cell lines harboring MLL translocations, with an IC_{50} of 2.7 nM, while showing no effect on wild-type MLL lines. In the MLL-rearranged MV4;11 leukemia cell line, M-1121 reduces HOXA9 and MEIS1 expression in a dose-dependent manner, with IC_{50} values of 10.3 nM. It is orally bioavailable and demonstrates significant antitumor efficacy *in vivo*, achieving tumor regressions at tolerable doses in both subcutaneous and disseminated models of MLL-rearranged leukemia. At a daily oral gavage dose of 100 mg/kg for 26 days, M-1121 reduced the average tumor volume from 157 mm^3 to 106 mm^3 by day 26, corresponding to a 32% reduction. Importantly, M-1121 induced no body weight loss or other signs of toxicity during or after the treatment.[61]

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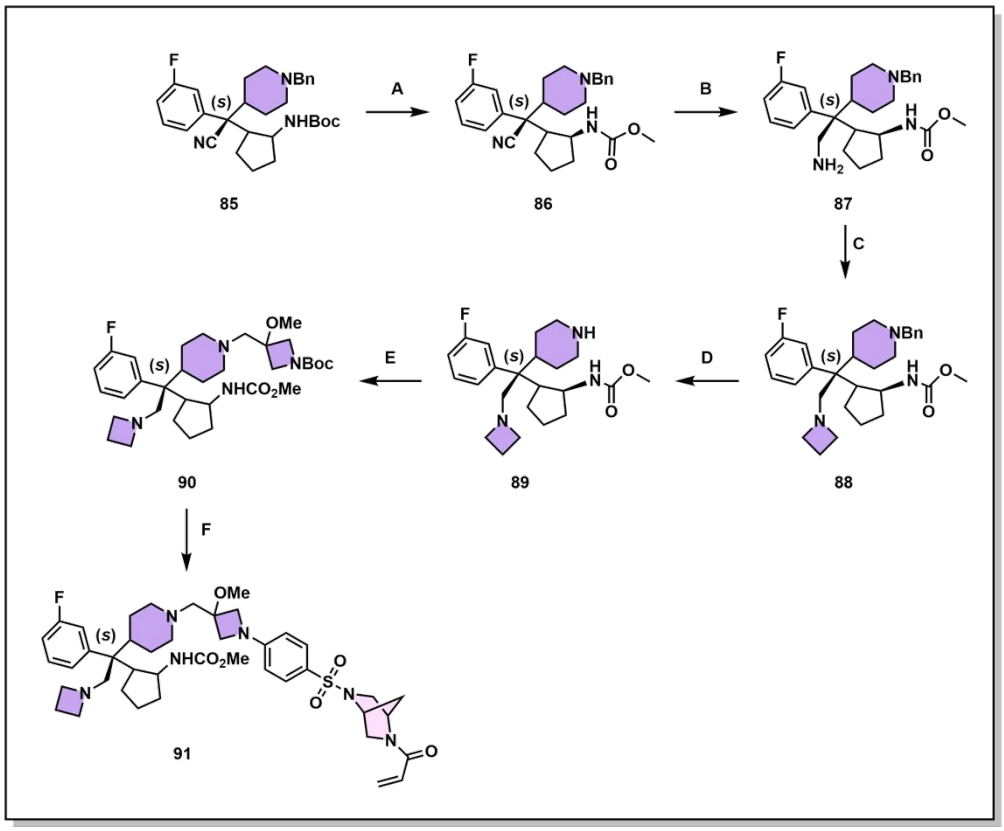

Scheme 14. Synthesis of a covalent Inhibitor of Menin-MLL Interaction containing 2,5-DBH. Reagents and conditions: A) 1,3-dibromopropane, K_2CO_3, KI, ACN, 80 °C, 89%; B) H_2, Pd/C, MeOH, 0 °C to rt, 4 h, 85%; C) K_2CO_3, KI, ACN, 80 °C, 2 h, 70%; D) TFA, DCM, rt, 2 h; E) K_2CO_3, DMSO, 80 °C, overnight, 52%; F) TFA, DCM, rt; acrylic anhydride, DIPEA, DCM, rt, 2 h, 80%.

4.2 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Diaza-heterocycles.

Diaza heterocycles encompass a range of cyclic structures containing two nitrogen atoms at varying positions. Common examples include pyrimidine, imidazole, pyridazine, pyrazole, piperidine, piperazine, and diazepine, all of which are well-established scaffolds in medicinal chemistry.[62–68] These compounds are recognized for their potency and versatility in drug development, playing a crucial role in the treatment of various diseases. This makes diaza heterocycles a highly attractive category for researchers focused on designing and developing new chemical entities, given their potential to yield novel therapeutic agents.

To optimize selective p21-activated kinase 1 (PAK1) inhibitors, McCoull *et al*. utilize a structure-based drug design approach to design a set of molecules. p21-activated kinases (PAKs) represent a family of serine/threonine kinases that are pivotal in

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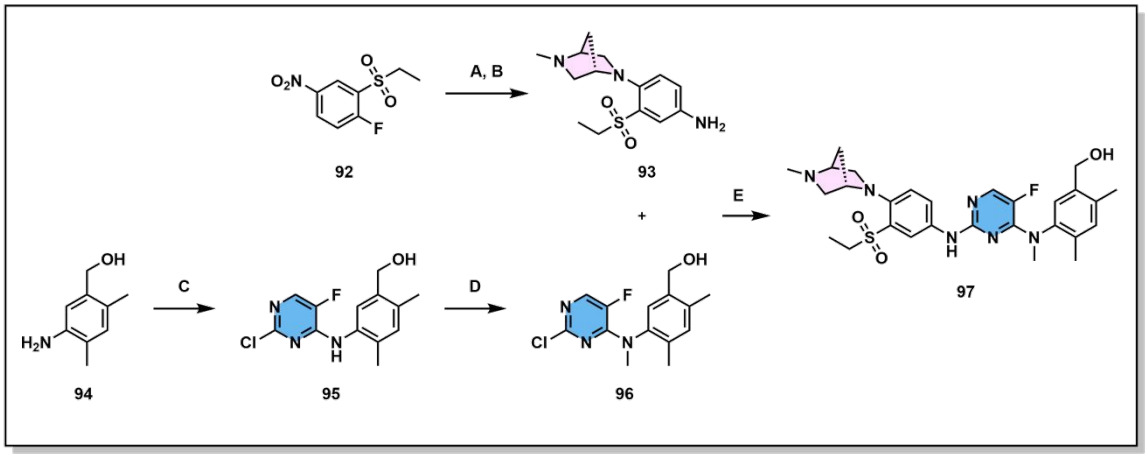
regulating numerous cellular functions, such as cell motility, morphology, survival, and proliferation. Functioning as downstream effectors of the Rho GTPases Cdc42 and Rac, PAKs integrate signals from these small GTPases to orchestrate cytoskeletal dynamics and modulate various signaling cascades.[69] McCoull and his team selected bis-anilino pyrimidine as the core structure for subsequent modifications. Guided by the findings from structure-based drug design (SBDD), various electron-donating groups (EDG) and electron-withdrawing groups (EWG) were strategically introduced at different positions on the parent scaffold. Additionally, several piperazine analogs, including 2,5-DBH, were chosen as secondary heterocyclic structures for further optimization (**Scheme 15**).[70] An *in vitro* inhibitory assay was conducted against PKA1, pPKA1, PAK4, KDR, FGFR1, and SRC kinases. Compound (**97**) demonstrated exceptional inhibitory potency, particularly against PKA1 and pPKA1, with an IC_{50} of 0.58 nM for PKA1 and 0.11 µM for pPKA1. These results position compound **(97)** as one of the most potent and selective compounds within the series. The *in vivo* pharmacokinetic parameters of compound **(97)** were also evaluated in mice. The compound exhibited low intrinsic clearance (Cl_{int} = 11 µL/min/10^6) and was characterized in a mouse pharmacokinetic profile. Oral administration achieved moderate clearance, with a maximum plasma concentration (C_{max}) of 7.7 µM following a 100 mg/kg dose.[70]



Scheme 15. Synthesis of pyrimidine-based 2,5-DBH. Reagents and conditions: A) 2-methyl-2,5-DBH, K_2CO_3, DMSO, 55 °C, 42%; B) Pd/C, H_2, EtOAc, EtOH, rt, 18 h, 93%; C) 2,4-dichloro,5-Fluoro-pyrimidine, DIPEA, 100 °C, 17 h, 77%; D) Cs_2CO_3, MeI, DMF, rt, 1 h, 79%; E) HCl, TsOH, IPA, 90 °C, 24 h, 47%.

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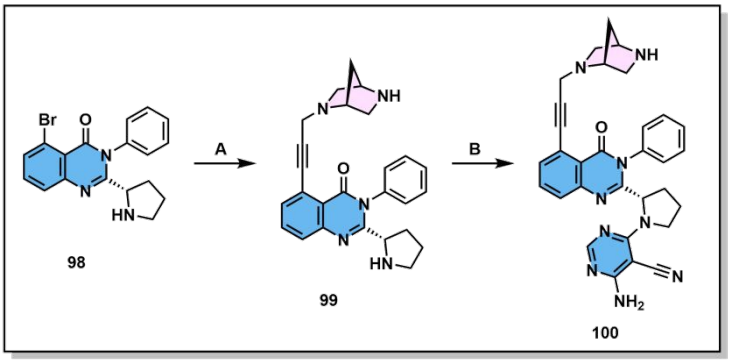
Drawing inspiration from the first FDA-approved Phosphoinositide 3-kinase δ (PI3Kδ) inhibitor, idelalisib, Wei *et al*. developed and optimized a series of 5-alkynyl-substituted PI3Kδ inhibitors. This series was designed to enhance potency and selectivity, building on the structural framework of idelalisib to achieve improved pharmacological properties. PI3Ks are a family of lipid kinases essential for regulating key cellular processes such as growth, metabolism, proliferation, and survival. PI3Kδ, a specific isoform within the class I PI3K family, is particularly important in modulating immune cell function. Due to its pivotal role, PI3Kδ has become a significant therapeutic target in the treatment of various hematological malignancies and inflammatory disorders.[71] PI3Kδ is a key player in the aberrant signal transduction pathways associated with B-cell malignancies, making it an attractive target for molecular therapies. Specific inhibition of PI3Kδ has emerged as a promising therapeutic approach for chronic lymphocytic leukemia (CLL).[72] Building on this approach, Wei and co-workers synthesized multiple series based on a 5-alkynyl-substituted quinazolinone ring (**Scheme 16**). [73] All newly synthesized compounds were evaluated for their activity against PI3Kδ and against the proliferation of (SU-DHL-6 B-cell) leukemia cells. Compound (**100**) containing 2,5-DBH and quinazolinone ring showed reasonable potency against PI3Kδ with an IC_{50} value of 135 nM. *In vitro* anti-proliferative assay against SU-DHL-6 B-cell showed that (**100**) inhibited proliferation at 1260 nM.[73]



Scheme 16. Synthesis of quinazolinone-based 2,5-DBH derivative. Reagents and conditions: A) (1*S*,4*S*)-2-(prop-2-yn-1-yl)-2,5-DBH, CuI, $Pd(PPh_3)_2Cl_2$, DEA, DMF, 120 ºC, 20 min, 47%; B) 4-amino-6-chloropyrimidine-5-carbonitrile, n-BuOH, DIPEA, M.W., 130 ºC to 160 ºC, 20 min 74%.

In 2017, Cernak *et al*., described the application of micromole-scale high-throughput experimentation in the early drug discovery phase to enable the lead identification and optimization of diacylglycerol acyltransferase 1 (DGAT1) inhibitors. Diacylglycerol O-

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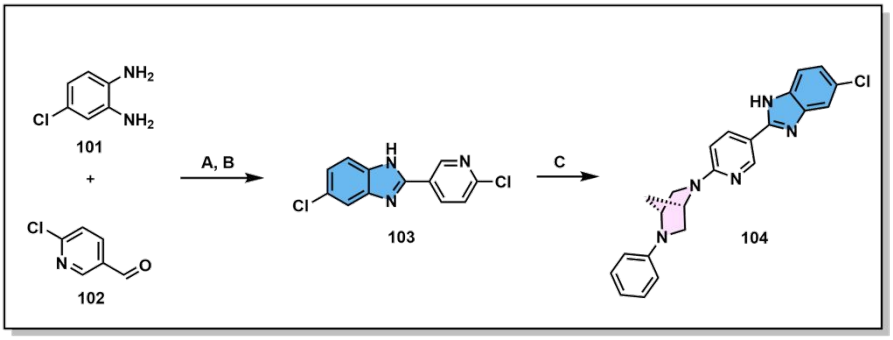
acyltransferase 1 (DGAT1) is an enzyme that plays a crucial role in the final step of triglyceride synthesis by catalyzing the conversion of diacylglycerol and fatty acyl-CoA to triglycerides. DGAT1 has been extensively studied as a therapeutic target for metabolic disorders like cancer and other disorders related to lipid metabolism due to its importance in regulating lipid metabolism.[74] To explore DGAT1 inhibitors, Cernak and co-workers selected benzimidazole as the core structure for further modification (**Scheme 17**).[75] *In vitro* enzyme inhibition assays on hDGAT1 were conducted to evaluate the potency of all the synthesized compounds. The compound featuring benzimidazole coupled with 2,5-DBH (**104**) exhibited lower inhibitory activity, suggesting a weaker interaction with the enzyme. In contrast, the benzimidazole-spiro compounds displayed significantly enhanced potency, with IC_{50} values in the nanomolar range.[75]



Scheme 17. Synthesis of benzimidazole coupled with 2,5-DBH. Reagents and conditions: A) THF, air 19%; B) DMF and H_2O, solid Oxone, rt, open air 3 h, 75%; C) DIPEA, DMA, tert-butyl (1*S*,4*S*)-5-phenyl-2,5-DBH-2-carboxylate, 140 °C, M.W., 12 h, 5%.

Llona-Minguez *et al*. reported a series of substituted pyridazine derivatives as novel and potent dCTPase inhibitors. dCTPase, or deoxyribonucleotide triphosphate pyrophosphatase, is an enzyme that catalyzes the hydrolysis of deoxycytidine triphosphate (dCTP) to deoxycytidine monophosphate (dCMP) and inorganic phosphate. This reaction is crucial in nucleotide metabolism and plays a significant role in regulating the levels of dCTP within the cell, which is essential for DNA synthesis and repair.[76] The core structure, pyridazine, was modified by dividing it into two different categories, left-hand side (LHS) and right-hand side (RHS) regions. 2,5-DBH was part of the LHS modifications (**Scheme 18**). Notably, (**108**) exhibited strong inhibition against the dCTPase enzyme, with an IC_{50} of 1.7 μM in the micromolar range. The binding efficiency index (BEI = pIC_{50}/MW) was found to be 12.5.[77]

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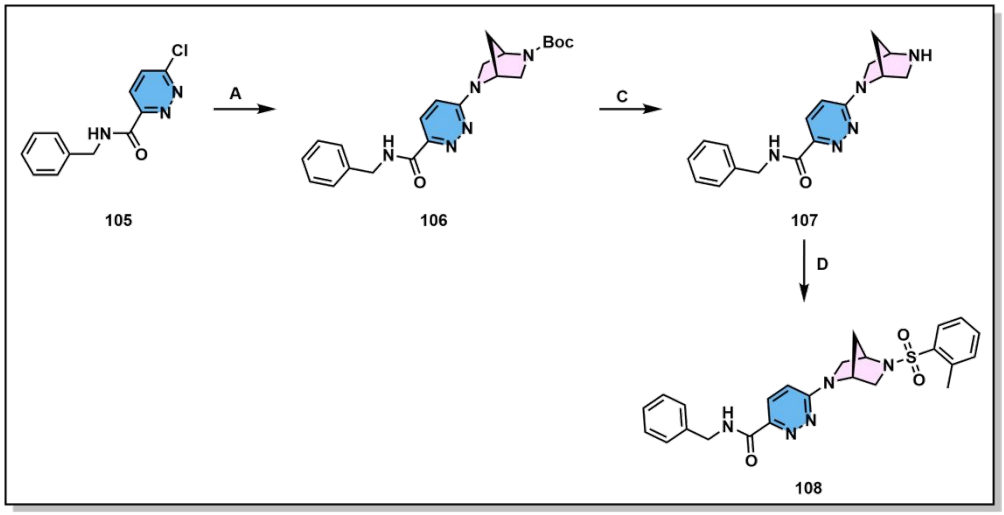

Scheme 18. Synthesis of pyridazine containing 2,5-DBH. Reagents and conditions: A) tert-butyl (1*S*,4*S*)-5-phenyl-2,5-DBH-2-carboxylate, TEA, 1,4-dioxane, 100 °C, 18 h, 54%; B) 4-M HCl in 1,4-dioxane, rt, 18 h, 86%; C) 2-methylbenzenesulfonyl chloride, TEA, rt, 18 h 68%.

Small-molecule-based antibacterial drugs are essential for combating pathogenic microorganisms. However, the widespread overuse of antibiotics in both medical treatments and animal husbandry has contributed to the growing threat of multidrug-resistant bacterial infections. Antimicrobial resistance has become a critical global health crisis that demands immediate attention. The rapid development of resistance is steadily reducing the effectiveness of existing antibiotics, jeopardizing their ability to treat bacterial infections.[78] To address this challenge, developing novel antibacterial agents with new mechanisms of action is vital. Without intervention, the continuous evolution of resistant strains will further undermine antibiotic efficacy, threatening the foundation of modern medical treatments.[79] Therefore, innovation in antibacterial drug discovery is crucial to ensure long-term success in battling resistant infections. Based on structure-based virtual screening, Fang *et al*. synthesized a series of novel 2,4-disubstituted-6-thiophenyl-pyrimidine derivatives and investigated their antibacterial activities against clinically relevant pathogens (**Scheme 19**). Filamenting temperature-sensitive mutant Z (FtsZ) is a critical protein involved in bacterial cell division and plays a pivotal role in the formation of the Z ring, which is essential for cytokinesis in prokaryotes. Inhibiting FtsZ function could disrupt bacterial proliferation and has emerged as a potential target for novel antibacterial agents.[80] Fang and colleagues designed a four-step synthetic pathway for the production of thiophen-2-ylpyrimidine

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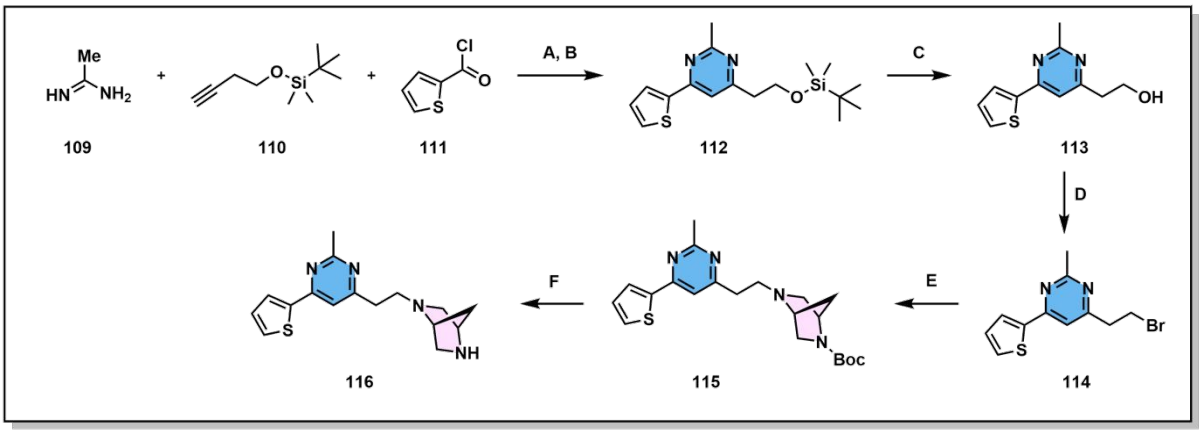
derivatives, incorporating different cyclic amine moieties, including 2,5-DBH (**Scheme 19**). The antibacterial activities were evaluated against the panel of drug-sensitive bacterial strains, including *B. subtilis* 168, *S. aureus* ATCC 29213, *E. coli* ATCC 25922, *E. faecium* ATCC 49624, *E. faecalis* ATCC 29212, and *S. epidermidis* ATCC 12228. Using a standard two-fold microdilution assay in Mueller-Hinton broth. For reference, berberine, methicillin, and vancomycin were tested under the same conditions. The compound featuring thiophen-2-yl-pyrimidine coupled with 2,5-DBH (**116**) exhibited a lower MIC compared to the standard.[81]



Scheme 19 Synthesis of thiophenyl-pyrimidine-based 2,5-DBH derivatives. Reagents and conditions: A) $Pd(PPh_3)_2Cl_2$, CuI, TEA, THF, rt, 1-2 h; B) Na_2CO_3, reflux, 14 h, 87%; C) PPh_3, CBr_4, THF, rt 3-4 h, 91%; D) conc. HCl, MeOH, rt 2 h, ; E) tert-butyl-(1*S*,4*S*)-2,5-DBH-2-carboxylate, ACN, rt. 24 h, 39%; F) TFA, DCM, rt, 4 h, 76%.

Wang and his team designed and synthesized novel anti-TB agents based on *N*-benzylic imidazo[1,2-a]pyridine carboxamides, which were subsequently evaluated for their activity against *Mycobacterium tuberculosis* strains, resulting in the synthesis of the desired 2,5-DBH compound (**127**) (**Scheme 20**). In the *in vitro* anti-MTB activity assessment, compounds were screened against MTB-H37Rv, MDR-MTB1, and MDR-MTB2 strains using the Microplate Alamar Blue Assay. The compound containing 2,5-DBH was specifically tested against the MTB-H37Rv strain. Although this compound (**127**) did not match the MIC values of standard drugs such as Q203, PBTZ169, rifampicin (RIF), and isoniazid (INH), it still inhibited the strain at low concentrations, with a MIC value of 0.452 μM.[82]

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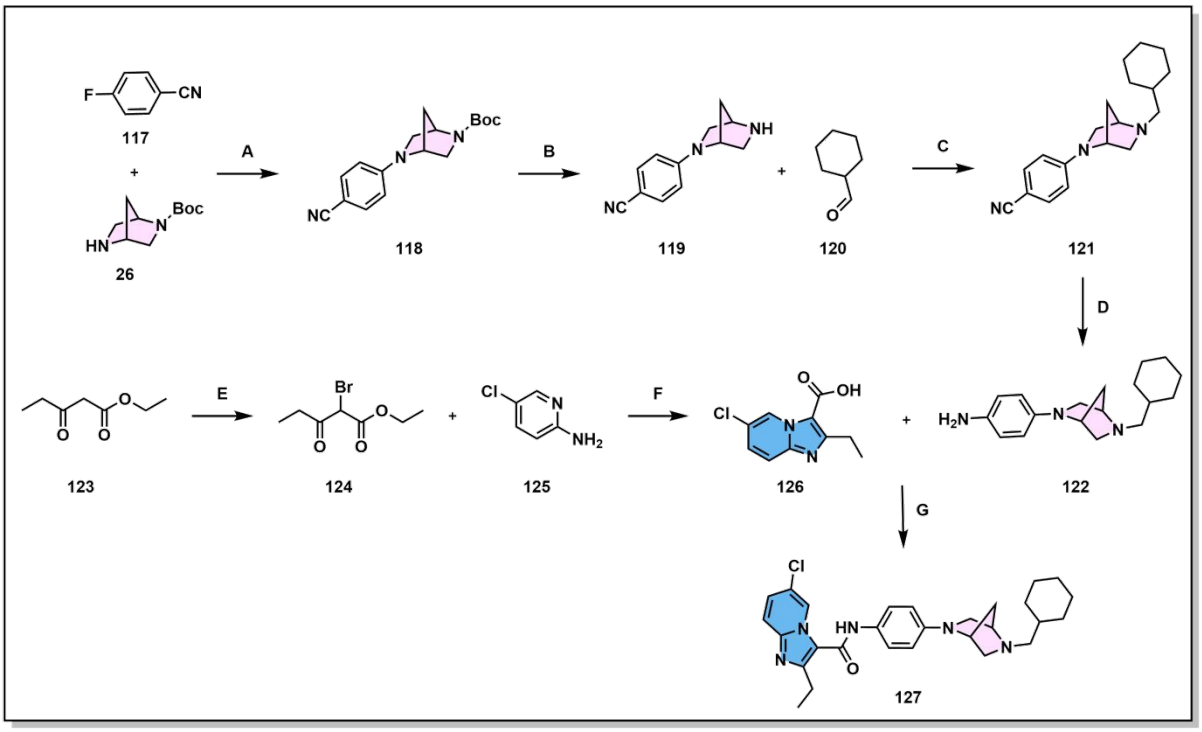

Scheme 20. Synthesis of imidazo[1,2-a]pyridine linked with 2,5-DBH. Reagents and conditions: A) K_2CO_3, DMSO, 80 ºC, 4 h, 45%; B) TFA, DCM, rt, 1 h, 80%; C) cyclohexanecarbaldehyde, $NaBH(OAc)_3$, AcOH, DCM, rt, 2 h, 60%; D) $LiAlH_4$, THF, rt, 4 h, 75%; E) NBS, NH_4OAc, Et_2O, rt, overnight; F) EtOH, M. W. 120 ºC, 0.5 h; G) BOP-Cl, TEA, DCM, rt, overnight, 21%.

Huang *et al*. reported the design, synthesis, and biological evaluation of various quinazoline-piperazine analogs derivatives as oral Cyclin-Dependent Kinase (CDK) inhibitors targeting hematological malignancies. Hematological malignancies, commonly known as blood cancers, include a variety of cancers that impact the blood, bone marrow, and lymphatic system. These malignancies are primarily categorized into three main types: leukemias, lymphomas, and multiple myeloma.[83] CDKs are serine/threonine kinases identified as promising therapeutic targets for cancer treatment. When complexed with cyclins, these proteins are essential regulators of cell cycle progression. Notably, most CDKs exhibit significantly elevated expression in cancerous tissues compared to normal tissues, making them attractive targets for anticancer strategies.[84] CDK9, a member of the cyclin-dependent kinase family, plays a crucial role in both the pathogenesis and treatment of hematological malignancies. As a key component of the positive transcription elongation factor b (P-TEFb) complex, CDK9 is essential for the transcriptional regulation of genes that control cell survival and proliferation. In many hematological cancers, CDK9 is frequently overexpressed,

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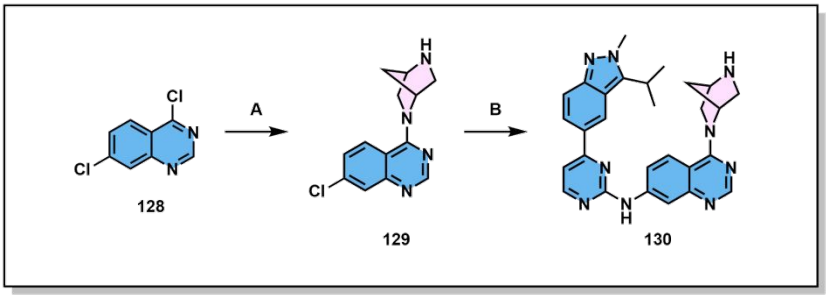
resulting in elevated levels of anti-apoptotic proteins such as MCL-1 and MYC. This overexpression supports tumor growth and survival by inhibiting apoptosis, thereby contributing to cancer progression.[85,86] To target CDK9, Huang and co-workers designed and synthesized a diaza-heterocycle containing 2,5-DBH (**130**) (**Scheme 21**). The synthesized compounds were biologically evaluated for their activity against CDK9 kinase and MV4-11 cells, with alvociclib and dinaciclib selected as the reference standard for comparison. Compound (**130**) exhibited notable potency and selectivity *in vitro* against CDK9 kinase, with an IC_{50} value of 5.1 nM. However, it did not surpass the IC_{50} of the standard Dinaciclib, which has an IC_{50} of 2.6 nM. In the MV4-11 cell inhibition assay, compound (**130**) outperformed the standard alvociclib, demonstrating an IC_{50} of 0.031 μM compared to alvociclib's IC_{50} of 0.079 μM.[87]



Scheme 21. Synthesis of indazol-5-yl-pyrimidin-2-yl-quinazolin coupled with 2,5-DBH. Reagents and conditions: A) 2,5-DBH, TEA, DCM, rt, 12 h, 52.5%; B) $Pd_2(dba)_3$, Brettphos, *t*-BuOK, Toluene, 100 °C, 4−8 h, 75%.

In the pursuit of discovering potent and selective Fms-like tyrosine kinase 3 (FLT3) inhibitors capable of overcoming clinically relevant resistance mutations, Wang *et al.* designed small-molecule inhibitors targeting FLT3, a receptor tyrosine kinase that plays a central role in hematopoiesis by regulating the proliferation and differentiation of hematopoietic progenitor cells.[88] Dysregulation of FLT3 signaling is strongly implicated in leukemogenesis, and FLT3 mutations are detected in approximately 30% of patients with acute myeloid leukemia (AML).[89,90] These mutations are primarily classified as internal tandem duplications (FLT3-ITD) or point mutations within the tyrosine kinase domain (FLT3-TKD). Clinically, FLT3-ITD mutations are associated with particularly poor prognosis, with reported hazard ratios for overall survival of approximately 1.5–2.0 compared to FLT3-wild-type AML, relapse rates of 50–70%, and reduced remission rates. In contrast, FLT3-TKD mutations generally confer a

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more moderate prognostic impact, with hazard ratios near 1.0–1.3 and relapse rates comparable to or slightly higher than those of FLT3-wild-type AML, depending on co-mutations and treatment context.[91]

To address this issue, Wang and fellow researchers designed a series based on 3-aminopyrazole-5-benzimiidazole (**Scheme 22**). The 3-aminopyrazole acted as the hinge region, interacting with residues like Cys694 and Glu692. The 5-benzamidazole portion was the hydrophobic region. The 2,5-DBH moiety rendered solvent access while interacting with FLT3. As a whole, the 3-Aminopyrazole-5-benzimidazole linked 2,5-DBH inhibits FLT3. Compound (**136**) featuring 2,5-DBH was biologically evaluated against the MV4-11 and BaF3-FLT3-ITD-F691L cell lines. FN-1501 and quizartinib were chosen as reference standards for comparison in these evaluations. Cell viability was assessed using the CellTiter-Glo luminescent assay, and IC_{50} values were calculated against MV4-11 cells. Compound (**136**) emerged as one of the most potent compounds, with an IC_{50} of 2.26 ± 0.39 nM, surpassing the reference standard FN-1501, which had an IC_{50} of 6.38 ± 0.69 nM. This was a result of an extensive SAR studies whereby, the necessary core scaffold in the hinge region was retained and progression towards the potent moiety was achieved via substitutions of benzodioxol in the hydrophobic region leading to benzoimidazole, substitutions of the introduced benzoimidazole for increased interaction in the ribose region and substitution of the 4-piperidyl at the solvent region. However, compound (**136**) failed to effectively inhibit the growth of BaF3-FLT3-ITD-F691L cells Notably, only the piperazine-based derivatives retained appreciable inhibitory activity against the mutant cell line, highlighting the sensitivity of FLT3 resistance profiles to linker and solubilizing group selection.[92]

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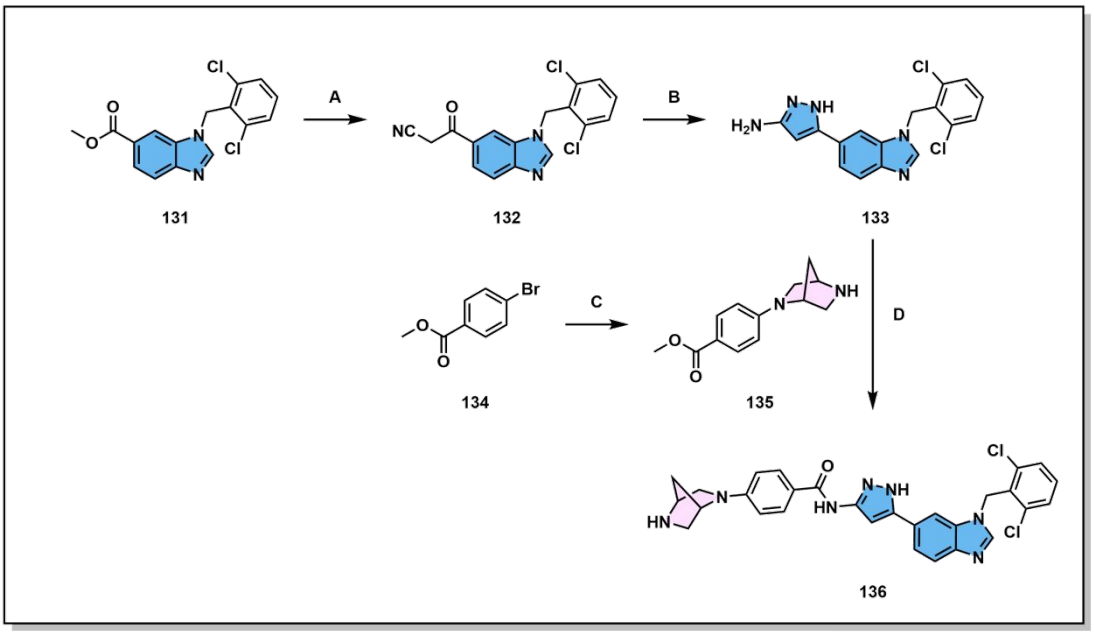

Scheme 22. Synthesis of 3-Aminopyrazole-5-benzimidazole based 2,5-DBH derivative. Reagents and conditions: A) ACN, 60% (w/v) ice cooled NaH suspension, THF, reflux, 7h; B) hydrazine monohydrate, EtOH, reflux under a N_2 atmosphere, 6 h; C) *N*-Boc-2,5-DBH, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 °C, 6 h under a N_2 atmosphere; D) $Al(CH_3)_3$, toluene, reflux under a N_2 atmosphere, 8 h, overall yield 13% including all steps.

In an effort to combat Amyotrophic Lateral Sclerosis (ALS), Craig *et al*. designed a series of compounds aimed at selectively and potently inhibiting Dual Leucine Zipper Kinase (DLK) and Leucine Zipper-Bearing Kinase (LZK).[93] ALS is an idiopathic and fatal neurodegenerative disorder that affects the human motor system, leading to progressive muscle weakness, paralysis, and eventual respiratory failure.[94] DLK, also known as MAP3K12, and LZK, also known as MAP3K13, are members of the mixed lineage kinase family.[95] They play significant roles in neuronal signalling, particularly in response to stress and injury. Both DLK and LZK act as mitogen-activated protein kinase (MAPK) kinase kinases (MAPKKKs), activating downstream pathways that include c-Jun N-terminal kinase (JNK) and p38 MAPK. These pathways are crucial for cellular responses to various stimuli, including injury.[96] Notably, knockout of both DLK and LZK leads to enhanced neuroprotection, making them promising therapeutic targets for treating ALS. Craig and co-workers employed ligand- and structure-based drug design to identify various modifications on the core pyrimidine scaffold. Multiple series of compounds were designed and synthesized, one of which featured amino-pyrazine-pyrimidine as the core structure, along with various piperazine analogs (including 2,5-DBH) (**Scheme 23**). The synthesized compounds were biologically tested in DLK and LZK cell-based and biochemical assays. Among them, compound

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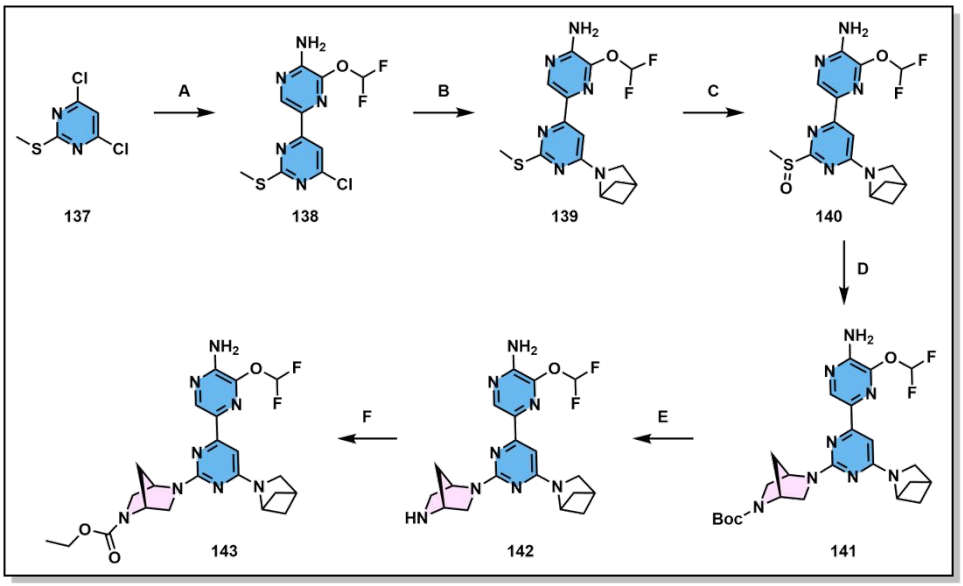
(**143**), featuring a diaza heterocyclic core linked to the 2,5-DBH group, demonstrated notable potency against DLK (IC_{50} = 2 nM) and LZK (IC_{50} = 13 nM), as well as their downstream targets DLKp-c-Jun (EC_{50} = 4.0 nM) and LZKp-c-Jun (EC_{50} = 157 nM). Additionally, the pharmacokinetic evaluation showed a human liver microsomal clearance (HLM Cl_{hep}) of 11.1 mL $min^{-1}kg^{-1}$, and its permeability was reflected in the MDR1-MDCK BA/AB ratio of 11.9 × 10^{-6} cm s^{-1}. These results highlight compound (**143**)'s significant activity across multiple assays, suggesting its potential as an effective inhibitor of DLK and LZK pathways.[93]



Scheme 23. Synthesis of amino-pyrazine-pyrimidine coupled with 2,5-DBH. Reagents and conditions: A) 3-(difluoromethoxy)-5-(trimethylstannyl)pyrazin-2-amine, $Pd(PPh_3)_4$, DMF, 110 °C ,2 h, 73%; B) 2-azabicyclo[2.1.1]hexane, HCl, K_2CO_3, DMSO, 80 °C, 5 h, 93%; C) *m*-CPBA, THF, 20 °C ,2 h; D) *N*-Boc-2,5-DBH, K_2CO_3, DMSO, 120 °C, 16 h, 30%; E) HCl, EtOAc, 20 °C, 0.5 h; F) ClCOOEt, NMM, DCM, 0°C, 1 h, 34%.

Modukuri *et al.* employed DNA-encoded chemical library technology (DEC-Tec) to discover novel, first-in-class small molecule inhibitors that are both highly potent and selective for the bone morphogenetic protein receptor type II (BMPR2) kinase. Utilizing a library comprising billions of compounds, the researchers conducted a high-throughput screen against the isolated BMPR2 kinase domain, successfully identifying lead compounds with high specificity and binding affinity toward BMPR2.[97] Bone morphogenetic proteins (BMPs) constitute a subgroup within the transforming growth factor-beta (TGF-β) superfamily and multifunctional cytokines essential for numerous

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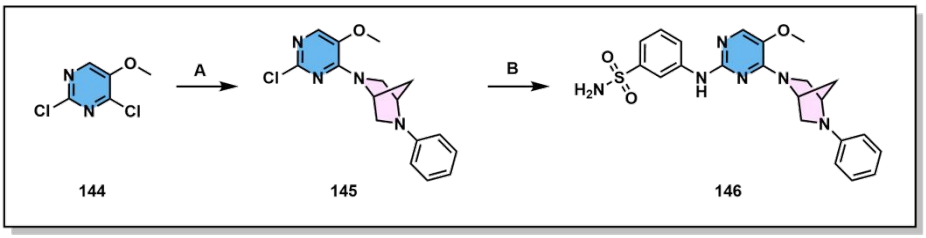
physiological processes, including osteogenesis, chondrogenesis, and tissue homeostasis.[98] BMP signaling is mediated through heteromeric receptor complexes composed of type I (ALK1, ALK2, ALK3, ALK6) and type II (ACVR2A, ACVR2B, BMPR2) serine/threonine kinase receptors.[99] Dysregulation of bone morphogenetic protein (BMP) signaling has been implicated in several severe human diseases, including fibrodysplasia ossificans progressiva (FOP), diffuse intrinsic pontine glioma (DIPG), pulmonary arterial hypertension, and vascular and gastrointestinal disorders. Importantly, signaling through mutant ALK2 requires functional BMP type II receptors highlighting the interdependence of type II receptors in pathological BMP signaling.[100] Although BMPR2 represents a compelling therapeutic node, its ubiquitous expression and involvement in multiple physiological processes pose significant challenges for selective inhibition.[101] To target BMPR2, Modukuri and co-researchers synthesized a series of sulfonamide-linked pyrimidines directly attached to various substituents including 2,5-DBH (**Scheme 24**). All synthesized compounds, including the 2,5-DBH-containing compound (**146**), were evaluated for their BMPR2 inhibitory activity. Compound (**146**) exhibited BMPR2 inhibition in the sub-micromolar range apparent (BMPR2 K_{iapp} IC_{50} = 930 nM), indicating measurable activity against the target. However, it was markedly less potent than its piperazinone-based counterpart within the same series, which displayed a substantially lower apparent BMPR2 K_{iapp} IC_{50} value of 2.8 nM, highlighting the superior BMPR2 inhibitory efficacy of the piperazinone scaffold.[97]



Scheme 24. Synthetic strategies for sulfonamide-linked pyrimidines containing a 2,5-DBH motif. Reagents and conditions: A) 2-phenyl-2,5-DBH, DIPEA, DMF, 40 °C to 80 °C, 12 h; B) Aminobenzenesulfonamide, BrettPhos G2, Cs_2CO_3, dioxane, 110 °C, M.W, 1 h, overall yield 52% including all steps.

Marisol Espinoza-Chávez *et al*. developed a series of compounds for the treatment of Chagas disease, which is caused by the parasite *Trypanosoma cruzi*, through a hit-to-lead exploration approach. This strategy involved identifying promising molecular

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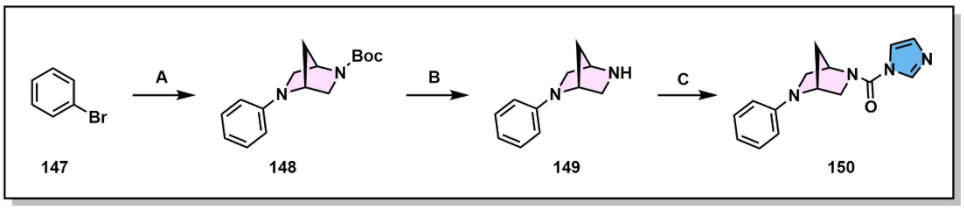
hits and optimizing their properties to enhance potency, selectivity, and drug-like characteristics, aiming to discover potential therapeutic agents for this protozoan parasitic disease. The designed compounds were synthesized via different synthetic routes. The compound featuring a diaza-heterocycle coupled with 2,5-DBH (**150**) (**Scheme 25**) was evaluated *in vitro* against *Trypanosoma cruzi* intracellular amastigotes (Tulahuen strain). The commercially available drug Benznidazole was used as a reference control in the phenotypic assays to benchmark the efficacy of the synthesized compounds. The compound featuring imidazole coupled with 2,5-DBH exhibited lower potency, with an IC_{50} value greater than 64 μM, in contrast to the reference standard Benznidazole, which showed an IC_{50} of 4.3 μM.[102]



Scheme 25. Synthesis of Imidazole linked 2,5-DBH. Reagents and conditions: A) $Pd_2(dba)_3$, BuO^tNa, XPhos, 1,4-dioxane, 100°C, 98%; B) 4-M HCl in Et_2O, DCM, rt.; C) 1*H*-imidazole-1-carboxylic acid CDI, DMF, rt, 73%.

Xu *et al*. discovered a series of pyrimidine-indazole-based CDK4 inhibitors by taking reference from the FDA-approved CDK4/6 inhibitors abemaciclib. The aim was to design inhibitors with greater selectivity for CDK4 over CDK6, achieving higher specificity in both enzymatic and cellular target engagement assays.[103] Cyclin-dependent kinases (CDKs) are a family of serine/threonine protein kinases that play crucial roles in regulating the cell cycle, transcription, and various cellular processes. Overactive CDKs can bypass normal cell cycle checkpoints, leading to unregulated growth. Mutations in genes encoding CDKs or their regulatory proteins further contribute to this dysregulation. Due to their critical role in cancer progression, CDKs have become promising targets for cancer therapies.[104] In this regard, Xu and fellow researchers synthesized a series of compounds featuring a pyrimidine-indazole core moiety with various piperazine analogs, coupled with amino-pyridine. A series containing diaza heterocycles coupled with 2,5-DBH was also prepared (**154**). (**Scheme 26**). The potency and selectivity of the compounds were evaluated through *in vitro* enzymatic assays and cell growth inhibition studies, providing insights into their

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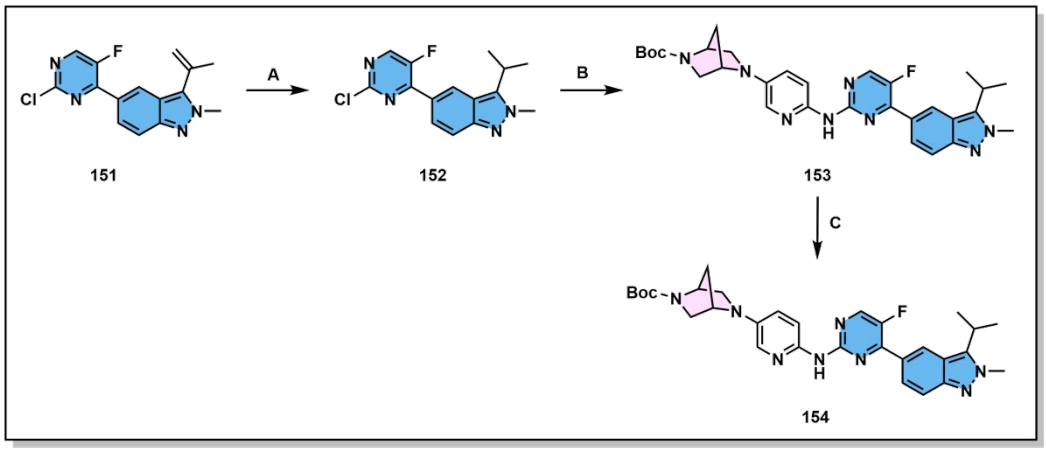
efficacy and target specificity. The enzymatic inhibitory activity was evaluated against the isozymes CDK2/cyclin A1, CDK4/cyclin D1, and CDK6/cyclin D1. The compound (**154**) featuring diaza heterocycles coupled with 2,5-DBH demonstrated enhanced potency in enzymatic inhibitory activity and selectivity. The IC_{50} values against the various enzymes were as follows: CDK4/cyclin D1 (IC_{50} = 0.28 nM), CDK6/cyclin D1 (IC_{50} = 0.39 nM), and CDK2/cyclin A1 (IC_{50} = 2.82 nM). The IC_{50} ratio of CDK6 to CDK4 was calculated to be 1.4, which was superior to that of the standard compounds Palbociclib and Abemaciclib. Cellular inhibitory potency was assessed using the MCF-7 cell line, an ER-positive, Rb-proficient breast cancer cell line, and the MDA-MB-436 cell line, an Rb-deficient breast cancer cell line. The compound (**154**) exhibited greater anti-proliferative potency against the MCF-7 cell line, with an IC_{50} of 56.0 nM, compared to an IC_{50} of 522.0 nM for the MDA-MB-436 cell line.[103]



Scheme 26. Synthesis of pyrimidine-indazole-linked 2,5-DBH. Reagents and conditions: A) $Rh(PPh_3)_3Cl$, H_2 (50 psi), THF, 50 °C, 24 h, 76%; B) tert-butyl 5-(6-aminopyridin-3-yl)-2,5-DBH-2-carboxylate, $Pd(OAc)_2$, Xphos, Cs_2CO_3, Dioxane, 110 °C, 18 h; C) TFA, DCM, 25 °C, 3 h.

4.3 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Triaza-heterocycles.

A heterocyclic system featuring three nitrogen atoms arranged in different positions may be classified within this category. In medicinal chemistry, triaza-containing heterocyclic systems have already demonstrated significant effectiveness against various diseases. However, research on the integration of triaza-containing

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heterocyclic systems with 2,5-DBH remains limited. Nonetheless, some studies in this area have yielded exceptional results.[105,106]

Lymphocyte Function-Associated Antigen-1 (LFA-1), a β2 integrin, interacts with ICAM-1 to mediate leukocyte adhesion and T cell activation, crucial for immune responses.[107] Dysregulation of the LFA-1/ICAM-1 interaction can lead to impaired immune responses, as seen in conditions like Leukocyte Adhesion Deficiency Type I (LAD I), where dysfunctional integrins result in compromised leukocyte recruitment and increased susceptibility to infections.[108] LFA-1 antagonists block LFA-1/ICAM-1 interactions, reducing leukocyte trafficking and inflammation. Since protein–protein interactions are difficult to target with small molecules, DNA-encoded library technology (DEL) enables efficient screening of vast chemical space through affinity selection, facilitating the discovery of novel therapeutic candidates.[109,110] Kollmann and his team first employed encoded library technology (ELT) to target this interaction, leading to the discovery of potent small molecules as LFA-1 antagonists with their ligand ICAM-1. The authors performed four different cycles of DNA-encoded libraries (DELs) in order to find the lead molecules. For the off-DNA synthesis of parent structure, they chose two primary scaffolds, 1,3,5-triazine and 2,5-DBH (**Scheme 27**). [111] The synthesized compounds were evaluated for their ability to inhibit the binding of ICAM-1 to LFA-1 using an ELISA-based ligand binding assay. Among them, compound (**160**) was the most potent, displaying an IC_{50} of 16 nM. A cell adhesion assay was then conducted to study the inhibition of LFA-1-mediated cell adhesion to ICAM-1. (**160**) exhibited potent inhibition of Jurkat cell adhesion to ICAM-1, both in the presence and absence of phorbol myristate acetate (PMA) stimulation. It also effectively inhibited the adhesion of K562 transfectants expressing wild-type (WT) LFA-1, as well as K562 cells expressing LFA-1 HA in the presence of dithiothreitol (DTT). However, it failed to inhibit mutant LFA-1 in the absence of DTT treatment. Based on the biological data, a detailed SAR was derived and is presented in (**Fig. 6**). Additionally, some molecules from this series were selected for further investigation by directly conjugating Cyanine3 (Cy3) dye to the DNA attachment point. Compounds were also synthesized with DNA headpieces and ligated to biotinylated DNA to facilitate the detection of their binding activity.[111]

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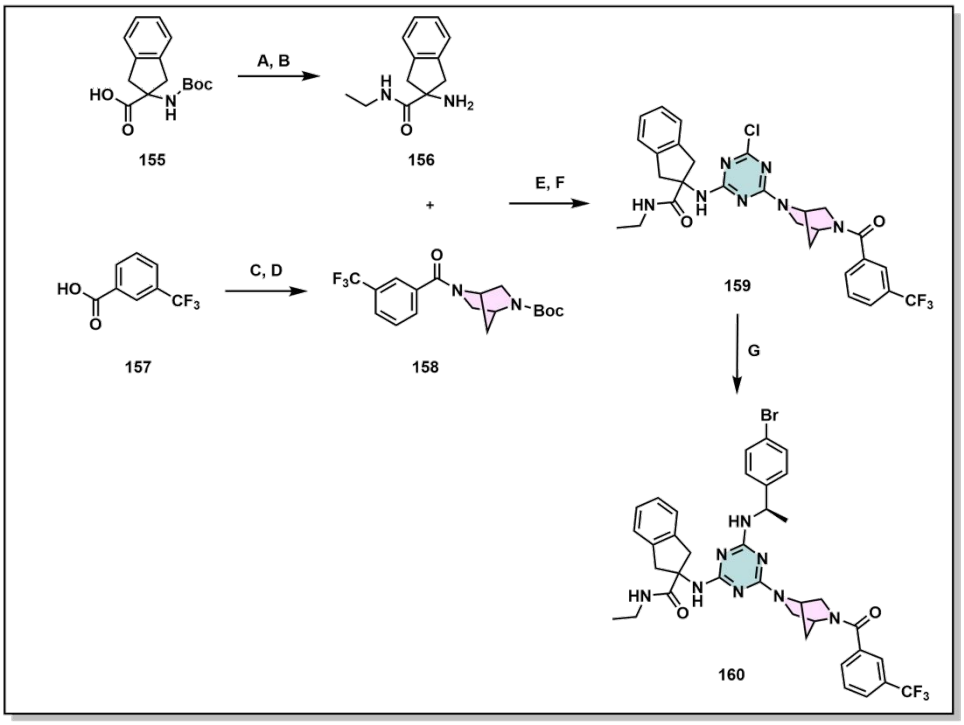

Scheme 27. Synthesis of 1,3,5-triazine-linked 2,5-DBH. Reagents and conditions A) ethylamine hydrochloride, HATU, DIPEA, DMF, rt, overnight, 99%; B) 20% TFA, DCM, rt, 2 h, 99%; C) DIPEA, DMF, rt, 2 h; D) 20% TFA, DCM, rt, 2 h; E) cyanuricchloride, DIPEA, ACN; F) DIPEA, ACN, rt, 2 h; G) DIPEA, ACN, 80 ºC, overnight, 53%.

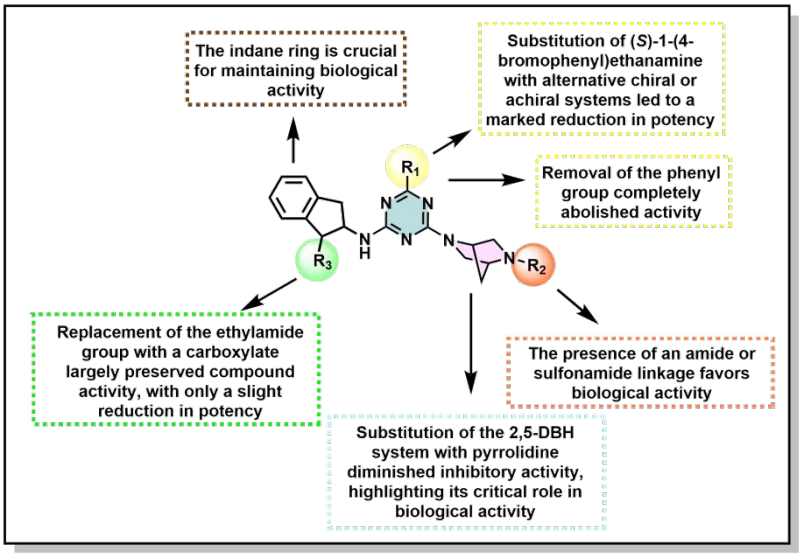

Fig. 6. SAR Studies of 1,3,5-triazine-linked 2,5-DBH derivatives.

As the aim was to discover spleen tyrosine kinase (SYK) inhibitors for solid tumor treatment, Wang *et al*. synthesized a series of novel derivatives based on imidazo[1,2-a]pyrazine coupled with 2,5-DBH.[112] SYK is a non-receptor protein tyrosine kinase that plays a crucial role in various signaling pathways. SYK is involved in the transduction

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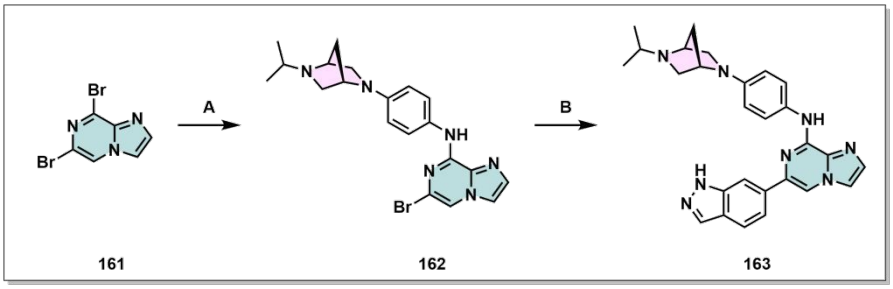
of signals from immune receptors, including B-cell receptors and Fc receptors, making it a key player in immune responses.[113] Studies have implicated that abnormal activation or dysregulation of SYK can contribute to tumor progression.[114] In solid tumors, SYK expression levels have been correlated with poor prognosis and aggressive disease characteristics.[115] Thus, Wang *et al*. developed novel SYK inhibitors based on imidazo[1,2-a]pyrazine derivatives to target solid tumors, given SYK's role in immune signaling and tumor progression. Using 6,8-dibromoimidazo[1,2-a]pyrazine and N-Boc-piperazine/polycyclic piperazine, they synthesized intermediates via DIPEA in isopropanol, followed by Suzuki-Miyaura coupling with heteroaryl-boronic esters to yield final compound (**163**, **Scheme 28**). These compounds showed >90% enzymatic SYK inhibition and demonstrated potent cytotoxicity (IC_{50}: 0.72–9.17 μM) against ovarian (SKOV3, HEY, ES2, OVCAR5, Cao3, SW626) and lung (A549, H1299, H460) cancer cell lines, outperforming entospletinib. *In vivo*, oral administration in SKOV3 xenograft mice at 10, 20, and 40 mg/kg inhibited tumor growth by 57.5%, 61.3%, and 76.7%, respectively. Biological studies enabled the establishment of a structure–activity relationship (SAR), which is summarized in (**Fig. 7**). Molecular docking confirmed strong SYK binding (PDB: 4PUZ), highlighting these derivatives as promising SYK-targeted antitumor agents.[112]



Scheme 28. Synthesis of imidazo[1,2-a]pyrazine coupled with 2,5-DBH. Reagents and conditions: A) DIEA, isopropanol, 85 °C, 94%; B) heteroaryl-boronic ester, $PdCl_2$(dppf), Na_2CO_3, 1,4-dioxane, 100 °C, under argon atmosphere overnight, 25%.

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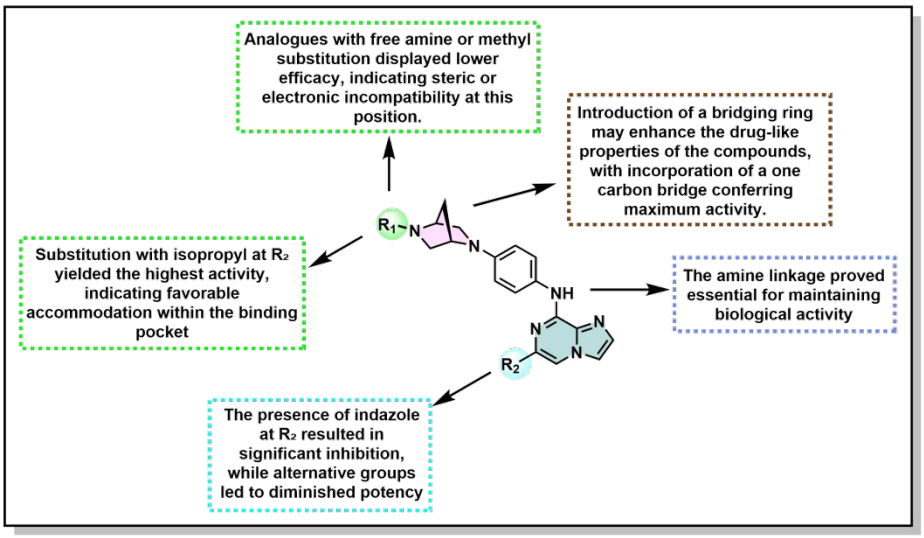

Fig. 7. SAR Studies of imidazo[1,2-a]pyrazine coupled with 2,5-DBH.

4.4 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Oxa-Aza-heterocycles.

A heterocyclic system containing at least one nitrogen and one oxygen atom in different ring positions is classified as an oxa-aza-heterocycle. Oxazole, oxazine, oxadiazole, benzoxazole, benzisoxazole, morpholine, etc.[116–121] contribute distinct bioactive properties relevant to therapeutic development, demonstrating significant effectiveness against various diseases. Studies reported that the design, synthesis, and biological evaluation of molecules incorporating both 2,5-DBH and oxa-aza-heterocycles have produced some promising compounds. These compounds exhibit potential across various therapeutic areas, showcasing the synergistic benefits of combining these structural elements in drug design.

Over the past several years, fatty acid amide hydrolase (FAAH) has garnered significant attention as a pivotal therapeutic target in the management of inflammation. As a key enzyme in the endocannabinoid system, FAAH regulates the levels of bioactive fatty acid amides, including anandamide (AEA).[122] Through the hydrolysis of AEA and related fatty acid amides, FAAH modulates critical physiological processes such as pain sensation, inflammation, and neuroprotection. Consequently, inhibition of FAAH elevates AEA levels, thereby enhancing analgesic and anti-inflammatory effects, which makes FAAH a promising therapeutic target for chronic pain, anxiety,

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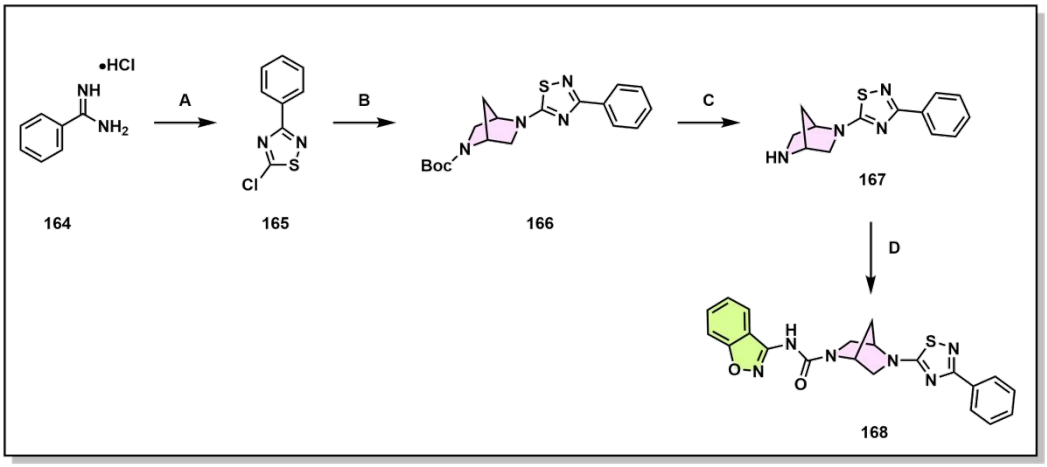
and neurodegenerative diseases. Building on this rationale, Kono *et al*. designed piperazine ureas–based FAAH inhibitors by coupling benzisoxazole with various piperazine analogs. The team synthesized various piperazine analogs, including 2,5-DBH (**168**), starting from benzamidine hydrochloride (**Scheme 29**). These compounds were screened for FAAH inhibition in human and rat enzyme assays. Results revealed that while the benzisoxazole–2,5-DBH analog showed lower activity(IC_{50} >1000 nM), the benzisoxazole–piperazine analog exhibited potent FAAH inhibition (IC_{50} 4.8 nM), underscoring the value of specific structural combinations for developing novel analgesic and anti-inflammatory agents.[123]



Scheme 29. Synthesis of benzisoxazole coupled 2,5-DBH. Reagents and conditions: A) perchloromethyl mercaptan, NaOH, DCM, H_2O, 0 ºC to rt, 2 h, 96%; B) *N*-Boc-2,5-DBH, TEA, DMF, rt, 30 min, 89%; C) THF, 2-N HCl in MeOH, rt, 12 h; D) 2,2,2-Trichloroethyl benzo[d]isoxazol-3-ylcarbamate, DIPEA, DMSO, 70 ºC, 3 h, 45%.

Meanwhile, Flanagan and colleagues developed a potent inhibitor targeting the aldo-keto reductase enzyme, with high selectivity for type 5, 17-β-hydroxysteroid dehydrogenase (AKR1C3). Aldo-keto reductase 1C3 (AKR1C3) belongs to the aldo-keto reductase (AKR) superfamily and plays a pivotal role in the metabolism of steroid hormones and various endogenous and exogenous compounds. AKR1C3 primarily acts as a 17β-hydroxysteroid dehydrogenase, catalyzing the reduction of Δ4-androstene-3,17-dione to testosterone and estrone to 17β-estradiol.[124] This enzymatic function positions AKR1C3 as a key regulator in steroid hormone biosynthesis and metabolism, influencing androgen and estrogen levels in tissues. AKR1C3 has been implicated in the progression of various cancers, including prostate, breast, and endometrial cancers.[125] By modulating steroid hormone levels, AKR1C3 can

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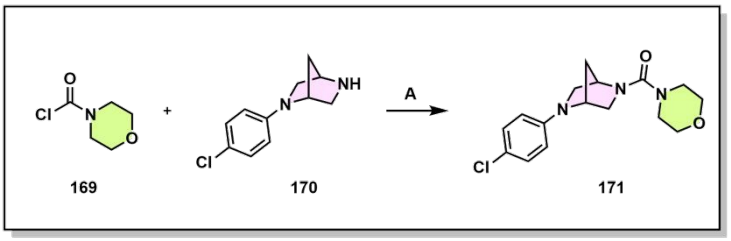
significantly impact cancer cell proliferation and survival, especially in hormone-dependent malignancies where its activity may contribute to tumor growth and resistance to treatment. The team designed a series of morpholine adducts incorporating various substituted piperazines, such as 2,5-DBH, homopiperazine, and 1,4-thiazinane (**171**) (**Scheme 30**). The inhibition assay of the synthesized compounds was conducted against the AKR1 isoforms C1–C4. The piperazine bridging unit (**171**) provided the appropriate conformational twist, allowing the benzene ring to optimally fit within the desired binding pocket. Among the tested compounds, the bridged piperazine (**171**) was one of the compounds that exhibited significantly greater potency and selectivity for the C3 isoform, demonstrating an IC_{50} of 3.7 μM for AKR1C3, while its inhibitory activity against the other isoforms was either abolished or markedly diminished.[126]



Scheme 30. Synthesis of 2,5-DBH coupled with morpholine. Reagents and conditions: A) DIPEA, DCM, 0 ºC to rt, 2 h, 77%.

4.5 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Thia-aza-heterocycles.

Systems known as thia-aza-heterocycles are those that include nitrogen (aza) and sulfur (thia). 2,5-DBH serves as a potent base or catalyst in the synthesis of thia-aza-heterocycles[127], which are valuable in materials science, agrochemicals, and pharmaceuticals.[128] The nucleophilicity and strong basicity of 2,5-DBH influence the stability and formation of these heterocycles, potentially altering their reactivity and facilitating efficient cyclization or other transformations. Thia-aza-heterocycles, such as thiazoles and thiazepines, are especially significant in drug design due to their biological activities.[129] These systems have a significant impact on the treatment of different ailments. Thus, researchers have started investigating this moiety.

Tanis *et al*. in 2012 reported a series of such moieties.[130] It was reported that the series housing this moiety can sufficiently inhibit leukotriene A4 hydrolase (LTA4H). The

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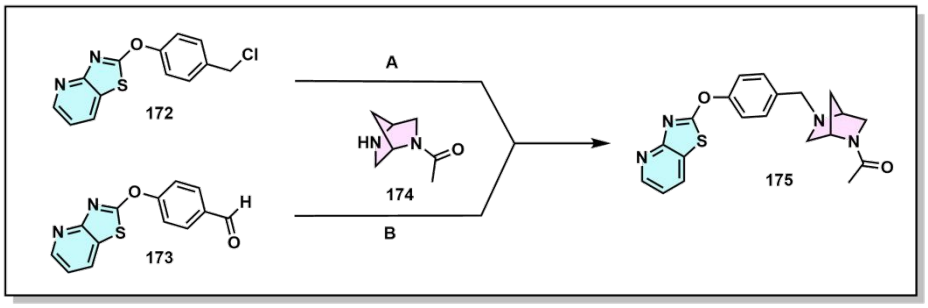
crystal structure of (LTA4H), a zinc-containing cytosolic enzyme having both hydrolase and aminopeptidase activity, was released in 2001.[131] LTA4H is an essential enzyme in the arachidonic acid cascade that occurs downstream of 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP). LTA4 additionally produces the leukotrienes LTC4, LTD4, and LTE4, often referred to as cysteinyl leukotrienes.[132] Leukotriene B4 (LTB4), a proinflammatory mediator, is produced when the unstable epoxide LTA4 is hydrolyzed by LTA4H, a stereospecific enzyme. In addition to activating neutrophils, LTB4 is a strong chemoattractant of mast cells, T-cells, eosinophils, dendritic cells, smooth muscle cells, and keratinocytes.[133–140] This series has exhibited an inhibitory effect on inflammation to a formidable extent. Benzothiazole-based LTA4H inhibitors showed strong MPO and LTB4 inhibition but suffered from hERG liability, highlighting the need for safer alternatives. In this regard, Tanis and co-workers synthesized a series (**Scheme 31**) which showed significant results on the biological evaluation. It was observed that compound (**175**) (where 2,5-DBH was used as the substituted secondary amine) was the most effective LTA4H inhibitor.[130] It showed a promising LTA4H IC_{50} of 1±1 nM. Also, the hERG liability was reduced (hERG dofetilide binding IC_{50} >10 μM). The reason for the increased potency was restricting the compounds within a very small range of lipophilicity, limiting backbone flexibility by shortening the tether and adding amines with extra polarity and/or stiff cage structures, reducing the hERG liability.[130]



Scheme 31. The synthesis of a 1-atom linker containing thiazolo[4,5-*b*]pyridines. Reagents and conditions: A) K_2CO_3, ACN, 50 ºC; B) $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt overall yield 15-53%.

The role of 2,5-DBH in reducing hERG liability has been evaluated by other researchers as well. In 2019, Lv *et al*. reported optimizations of antitubercular agents housing benzothiazinones.[141] It has been observed that benzothiazinones (BTZs), a

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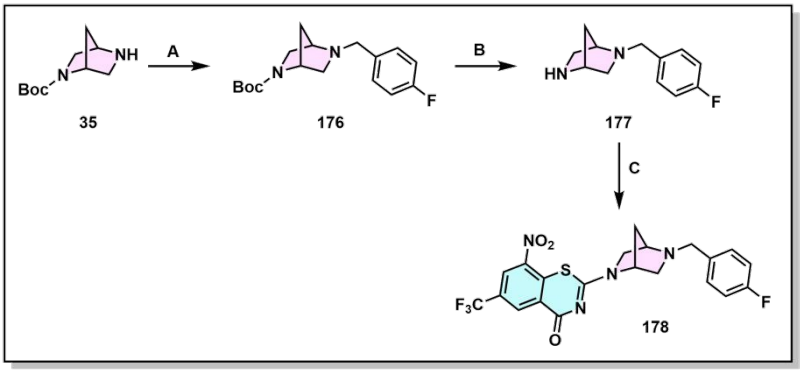
new family of TB medicines, exhibit substantial inhibitory activity against drug-sensitive MTB, MDR-MTB, and XDR-MTB strains.[142–147] BTZs target decaprenyl phosphoryl-b-D-ribose 2'-epimerase (DprE1). The most advanced candidates in this family, BTZ043 and PBTZ169 (formerly known as Macozinone).[148] They are presently undergoing Phase I (A single ascending dose study of BTZ043, NCT03590600) and Phase II (a Phase 2a study of PBTZ169, NCT03334734) clinical trials for the treatment of drug-susceptible TB and MDR-TB, respectively. The research group aimed at synthesizing a series of compounds from *N*-Boc-2,5-DBH (**Scheme 32**). Although other carboxylates were also employed in synthesizing this series, compound (**178**) emerged as a potent compound with depreciated hERG binding affinity. The MIC against MTB H37Rv was observed to be < 0.035 μM. In addition, the hERG binding affinity at 10 μM was found to be 94.3±0.6%.[141]



Scheme 32. Synthesis of benzothiazones containing 2,5-DBH. Reagents and conditions: A) 4-fluorobenzaldehyde or cyclohexanecarbaldehyde, $NaCNBH_3$, AcOH, rt to 50 ºC; B) DCM, TFA; C) 2-(methylthio)-8-nitro-6-(trifluoromethyl)-4H-benzo[*e*][1,3]thiazin-4-one, TEA, MeOH, overall yield 47%.

The most recent report was by Armani *et al*. in 2023.[149] They reported the discovery of several lysophosphatidic acid receptor 2 (LPA2) antagonists aiding in the alleviation of fibrotic disorders. Several of the derivatives contained the 2,5-DBH moiety, one prevalent aspect of chronic tissue damage, such as hepatic cirrhosis, renal fibrosis, and pulmonary fibrosis. Taken together, these conditions constitute a significant unmet clinical need.[150] One of the most prevalent types of idiopathic lung disorders (ILDs) is idiopathic pulmonary fibrosis (IPF).[151] Fibroblastic foci are at the forefront of fibrotic lung damage, and an idiopathic usual interstitial pneumonia (UIP) is a prerequisite for the diagnosis of IPF.[152] While nintedanib and pirfenidone, two antifibrotic medications already on the market, reduce the loss of lung function in patients, they do not affect

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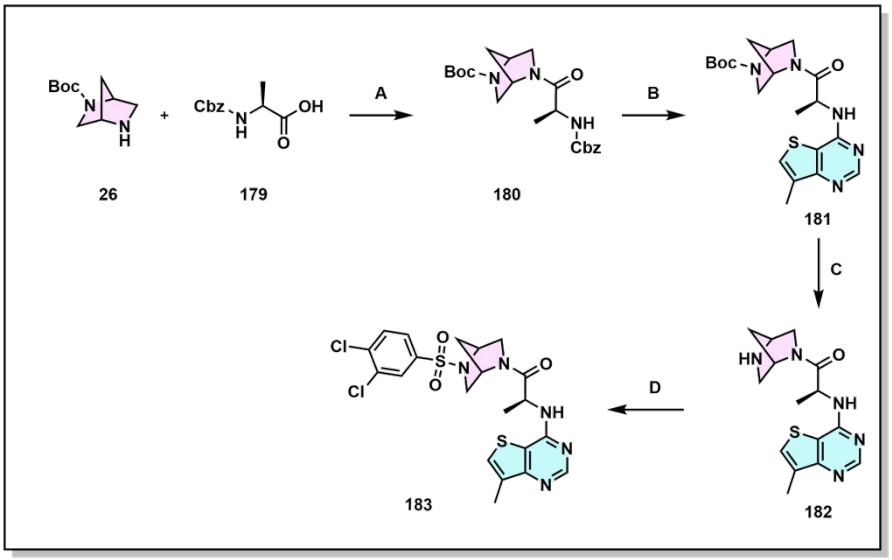
symptom management or quality of life.[153] Lysophosphatidic acid (LPA) is a bioactive phospholipid that regulates diverse processes, including cytoskeletal remodeling, proliferation, migration, and survival.[154] Amgen reported the first selective LPA2 antagonist as an anticancer agent. Armani *et al*. launched a medicinal chemistry program and began the synthesis of these derivatives and furnished compound (**183**) (**Scheme 33**).[149] This compound, when evaluated for human LPA1 and LPA2 inhibitory activity, exhibited an IC_{50} of 4.95 μM and 4.74 μM, respectively. Thus, this can be said that compound (**183**), housing the 2,5-DBH moiety, inhibited LPA1 and LPA2 successfully and can be considered for treating inflammation.[149]



Scheme 33. Synthesis of thieno[3,2-d]pyrimidine containing 2,5-DBH. Reagents and conditions: A) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt), DMF, r.t., 24 h, 100%; B) (1) H_2 (1 atm), Pd/C 10% w/w, EtOH, rt, 2−4 h, (2) 4-chloro-7-methylthieno[3,2-d]pyrimidine, DIPEA, ACN, 85 ºC, 24−48 h, 78%; C) (1) 4-M HCl in dioxane, DCM, rt, 4−12 h, (2) 3,4-dichlorobenzenesulfonyl chloride, pyridine, DCM, rt, 12−24 h, 62%; D) (1) BH_3- THF, rt, 3−12 h, then 60 ºC 2−12 h, (2) MnO_2, DCM, rt, 1−5 h, 16%.

4.6 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Substituted Phenyls.

The term "substituted phenyls" typically refers to various positions on the phenyl ring being modified.[155] The electronic nature and positional arrangement of substituents on phenyl rings—whether Electron-donating (–OH, $–OCH_3$, $–NH_2$) or electron-withdrawing ($–NO_2$, –COOH, –CN)—profoundly govern 2,5-DBH's electronic

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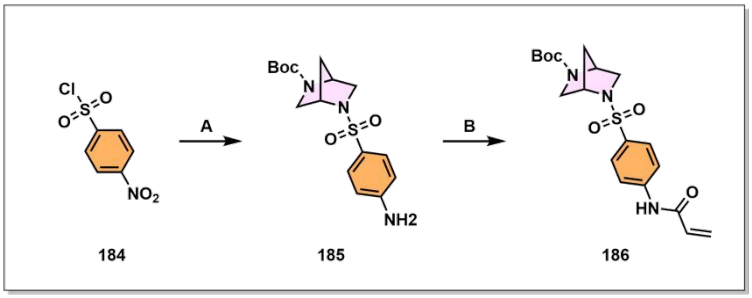
structure, chemical stability, and acidity, thereby dictating its molecular interactions and reactivity profile.[156,157]

In the year 2012, Prime *et al*. discovered a series of derivatives designed for the selective covalent inhibition of transglutaminase 2 for Huntington's chorea.[158] Tissue transglutaminase 2 (TG2, TGM2, human gene no. 7052) is a multifunctional enzyme that is mainly recognized for its ability to form isopeptide bonds between the γ-amino group of the lysine residue of the acyl-acceptor substrate and the γ-carboxamide of the glutamine residue of the acyl-donor substrate, which is a calcium-dependent intra- and intermolecular cross-linking activity.[159] Moreover, simple amidase, GTPase, ATPase, and protein disulfide isomerase activities have been shown to be displayed by TG2.[160–162] The transglutaminase family's most widely expressed protein has been shown to be distributed across the cytosol, cell nucleus, cell membrane, and extracellular compartments.[163,164] A function for TG2 activity in mitochondrial energy function is suggested by the genetic deletion of TG2 in mice.[165] The conditions that have been most strongly linked to TG2 overactivity include celiac disease and Huntington's disease, while evidence for its involvement in inflammation and cancer is also mounting.[166–168] This group aimed at designing derivatives with the 2,5-DBH along with other groups. (**Scheme 34**). Inhibition experiments using both wild-type and mutant variants of TG2 provided evidence for the direct covalent binding of screening hits to Cys277 of TG2. With the use of many computational models and the available open form X-ray crystal structure, the authors were able to increase the TG2 potency of the hits by more than two orders of magnitude while maintaining the isoform selectivity for other transglutaminases. Notable in this respect is compound (**186**), which demonstrated an IC_{50} of 2.1 and 14 μM potency against FXIIIa and TG1, respectively, with a TG2 IC_{50} of 0.30 ± 0.01 μM.[158]



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Scheme 34. Synthesis of Sulfonamidopiperazines containing 2,5-DBH. Reagents and conditions: A) DIPEA, THF, 2 h; B) Fe, NH_4Cl (aq), EtOH/H_2O (5:1), 80 ºC, 2 h; C) acryloyl chloride, DIPEA, THF, 18 h; overall yield quantitative.

López-Ortiz *et al*. reported the development of ranolazine-based derivatives containing the (1*S*,4*S*)-2,5-DBH in 2014.[169] Ranolazine is a clinically approved drug used for the treatment of chronic stable angina pectoris. It became the first new medication in over two decades to be approved for this condition when the U.S. FDA granted its approval in 2006.[170] By inhibiting the entry of Na^+ through the Na^+ slow channels, this medication works to prevent intracellular Ca^{2+} excess, which in turn prevents damage to the heart's cells, malfunction, and electrical activity instability.[171] Due to the need for new, more potent cardiovascular medications with fewer side effects, developing more effective pharmaceutical therapies is crucial to improving the quality of life for patients with cardiovascular illnesses. The synthesis of the targeted diazabicyclic analog's epimeric mixture is appended below (**Scheme 35**). The epimeric mixture [(*S,S,S*) (*S,S,R*)] **(191)** demonstrated vasodilatory activity in rat aortic rings, with IC_{50} values of log[M] 4.78 (with endothelium) and log[M] 63.59 (without endothelium). The vasorelaxant effect appears to arise from two mechanisms: endothelial NO release and a direct action on vascular smooth muscle. In addition, the mixture also promotes the release of vasoconstricting prostanoids through the cyclooxygenase pathway, an effect that is endothelium-independent. Pharmacological data further revealed that both (*S,S,R*) **(194)** and (*S,S,S*) **(196)** possess vasodilatory properties; however, compound (S,S,*R*) (**194**) uniquely triggers the release of vasoconstricting prostanoids via the cyclooxygenase pathway. Collectively, these findings suggest that the epimeric mixture [(*S,S,S*) (*S,S,R*)] (**191**) and compound (*S,S,S*) (**196**) display superior vasodilatory efficacy.[169]

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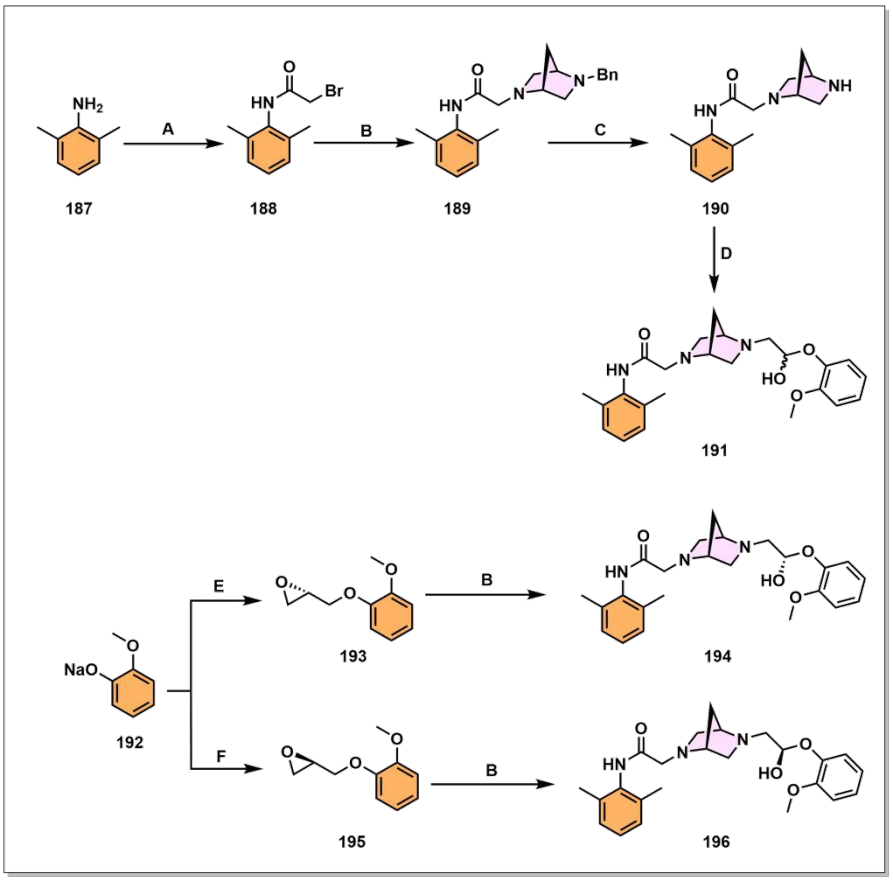

Scheme 35. Synthesis of ranolazine derivatives containing the (*1S,4S*)-2,5-DBH. Reagents and conditions: A) bromoacetyl bromide, TEA, DCM, -10 °C, 3 h, 88%; B) 2-benzyl-2,5-DBH, TEA, DCM, rt, 24 h, 90%; C) H_2, 10% Pd/C, MeOH, 60 psi, rt, 2 h, 99%; D) 2-(2-methoxyphenoxy)oxirane, TEA, MeOH, reflux, 12 h, 77%; E) (*R*)-epichlorohydrin, rt, 24 h, 86-95%; F) (*S*)-epichlorohydrin, rt, 24 h, 83%.

Canale *et al*. reported a series of of serotonin 5 receptor (5-HT_7Rs) antagonists bearing 2,5-DBH-derived arylsulfonamide scaffolds in 2016.[172] Through the stimulatory Ga12 proteins, these receptors, which are typical metabotropic receptors, or GPCRs, are favorably associated with adenylyl cyclase.[173] The central nervous system (CNS) and the distribution of 5-HT_7Rs (the thalamus, suprachiasmatic nuclei, and hippocampus) have been found to be correlated. This suggests that 5-HT7Rs are involved in physiological processes such as learning, memory, and the circadian rhythm, as well as in mood disorders, schizophrenia, anxiety, and the cognitive decline process.[174] 5-HT_7Rs antagonists have been demonstrated in several trials to mitigate cognitive impairment linked to CNS illnesses like schizophrenia.[175] Furthermore, several pieces of evidence have demonstrated that pharmacological inhibition of 5-HT_7Rs results in animal models exhibiting antidepressant-like behavior[176] indicating that 5-HT_7Rs antagonists may have therapeutic relevance for the treatment of

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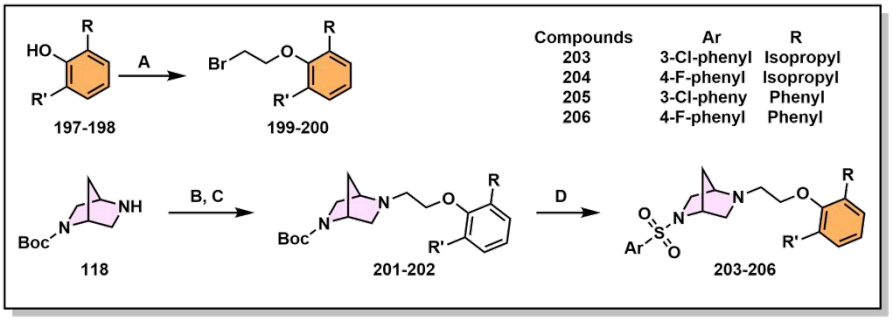
depression.[177,178] Lastly, the antagonistic interaction at the 5-HT$_7$Rs may contribute to the antidepressant effects of atypical antipsychotics such as amisulpride and lurasidone.[179,180] A multi-step process (**Scheme 36**) was used to synthesize the final arylsulfonamides (**203-206**). The biological evaluation of compounds 203–206 demonstrated measurable binding affinity toward the 5-HT$_7$ receptor, with K_i values in the range of 162–319 nM, as determined by radioligand binding assays using cloned human 5-HT$_7$ receptors expressed in mammalian cell membranes. In parallel, binding affinity toward the 5-HT$_1$A receptor was also assessed, yielding K_i values of 260–2667 nM. The comparatively weaker interaction with 5-HT$_1$A suggests a degree of selectivity toward 5-HT$_7$ within the limited receptor panel evaluated.[172]



Scheme 36. Synthesis of sulfonamide-based 2,5-DBH derivatives bearing substituted phenyl moieties. Reagents and conditions: A) 1,2-dibromoethane, K_2CO_3, KI, Acetone, 60 ºC, 48-72 h; B) K_2CO_3, KI, acetone, 60 ºC, 48-72 h; C) TFA/DCM (90/10; v/v), rt, 2 h; D) DCM, 0 ºC, 6-12 h; overall 30-70% yield including all steps.

In 2016, Gerstenberger *et al*. designed several modulators of bromodomain with compounds housing the 2,5-DBH moiety.[181] The ability of bromodomains to specifically identify ε-*N*-lysine acetylation patterns is crucial for the interpretation of these post-translational changes, which are significant elements of the "epigenetic code".[182] In oncology, where BET proteins control the production of important oncogenes, the recent identification of strong and highly selective inhibitors for the bromodomain and extraterminal domain (BET) family of bromodomains IV has sparked intense research interest.[183–187] To target this, Gerstenberger and his team synthesised a series of compounds (**Scheme 37**), ultimately developing compound (**210**) (PFI-3) by optimizing the initial fragment hit salicylic acid, and it is the first

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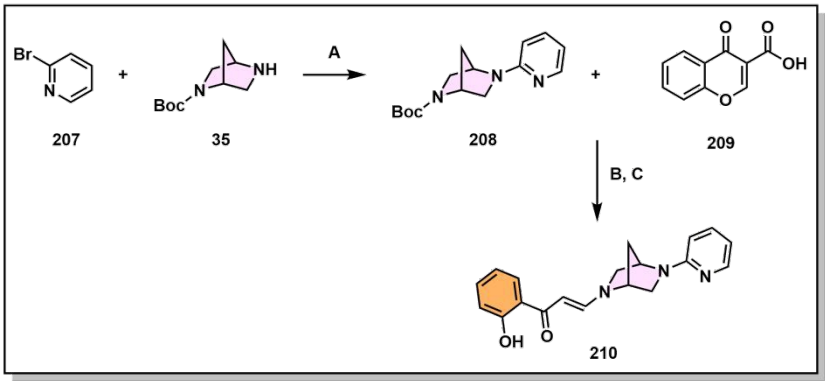
chemical probe of this kind for family VIII bromodomains. It has been applied to explore small-molecule-induced phenotypes in myoblasts and adipocytes through iterative library synthesis and structure-based design. Differential scanning fluorimetry (DSF) thermal shift analysis for compound **(210)** revealed markedly enhanced binding to PB1(5), SMARCA2 (both isoforms), and SMARCA4. The compound exhibited excellent stability, with a half-life of >250 h in PBS (pH 7.4, 20 °C). The strong Tm shift results were corroborated by isothermal titration calorimetry (ITC), yielding dissociation constants (K_D) of <100 nM for both PB1(5) and SMARCA4. Furthermore, compound (**210**) demonstrated complete selectivity over all non-family VIII bromodomains, as evidenced by both a 40-protein Tm shift panel and the BROMOscan screen (DiscoveRx).[181]



Scheme 37. Synthetic scheme of dibromophenol coupled 2,5-DBH derivative. Reagents and conditions: A) BINAP, $Pd(OAc)_2$, NaO^tBu, toluene, rt to 110 ºC 16 h; B) HCl, dioxane, DIPEA, EtOH; C) DIPEA, EtOH, rt.

In 2017, Mould *et al*. developed (4-Cyanophenyl)glycine derivatives as reversible inhibitors of lysine-specific demethylase 1 (LSD1).[188] Some of the compounds from the series also houses the potent 2,5-DBH. The first histone demethylase to be identified was LSD1, which has been shown to function as a transcriptional repressor in both normal and malignant cells.[189] LSD1 is a member of the FAD-dependent amine oxidase family of demethylases and catalyzes the demethylation of histone H3K4me1/2 and H3K9me1/2 lysine residues. Thus, the authors' goal was to create submicromolar LSD1 inhibitors that exhibit efficacy in cellular tests by employing in silico design to identify reversible LSD1 inhibitors through high-throughput screening. To address this limitation, Mould and his colleague synthesized a series of compounds, were compound (**216**, **Scheme 38**), among which compound (**216, Scheme 38**), incorporating the 2,5-DBH moiety, exhibited an IC_{50} value of **13.1 µM**

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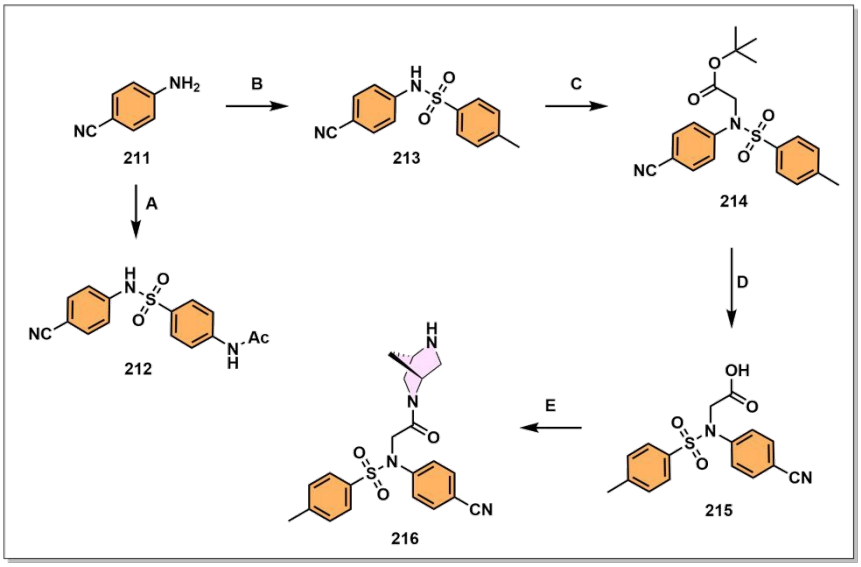
against LSD1 In addition, this compound showed a favorable binding affinity toward LSD1, with a K_d **of 2.4 µM**, as determined by surface plasmon resonance (SPR) analysis.[188]



Scheme 38. Synthesis of (4-Cyanophenyl)glycine derivatives as reversible inhibitors of LSD-1. Reagents and conditions: A) 4-acetamidobenzenesulfonyl chloride, DMAP, ACN, MW, 100 ºC, 1 h, 37%; B) 4-methylphenylsulfonyl, pyridine, ACN, rt, 12 h, 89%; C) tert-butyl bromoacetate, K_2CO_3, DMF, 1 h, 96%; D) TFA, DCM, 1 h, 98%; E) amine, DIPEA, COMU, DMF, then 4-M HCl/dioxane, rt, 75%.

The quest for a new class of antitumor agents that can effectively induce apoptosis without causing necrotic cell death presents a significant challenge in cancer research. In their study, Lasker *et al*. detail the multicomponent synthesis of seven novel (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-dithiocarbamates (**Scheme 39**), and evaluate their antiproliferative effects *in vitro* on a range of cancer cell lines, including cervical cancer (CaSki), breast cancer (MDA-MB231), lung cancer (SK-Lu-1), as well as human lymphocytes. Among the newly synthesized dithiocarbamates, compound (**219**) exhibited remarkable antiproliferative activity against CaSki, MDA-MB-231 and SK-Lu-1 tumour cell lines (with IC_{50} values 28, 18, and 20mg/mL, respectively) while notably avoiding any induction of necrotic cell death in both tumor cells and lymphocytes. Instead, compound (**219**) successfully triggered apoptosis in tumor cells through a caspase-dependent apoptotic pathway. Importantly, this compound also demonstrated a higher selectivity for tumor cells compared to human lymphocytes, suggesting its potential for therapeutic applications with minimized side effects.[190]

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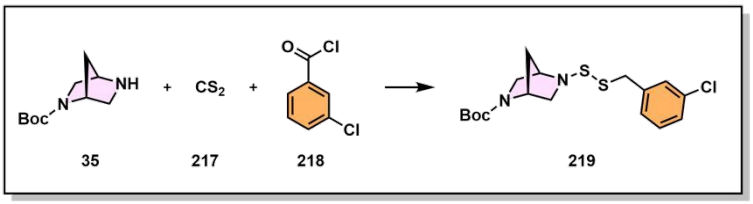

Schemes 39. Synthesis of dithiocarbamates containing DBH. Reagents and conditions. A) MgO, MeOH. 0°C to rt, 60%.

Laskar *et al*. synthesized six Michael adducts of (1*S*,4*S*)-2,5-DBH-dithiocarbamate with nitrostyrenes in 2018 and reported their antiproliferative activity against cervical cancer cells.[191] Since chemotherapy for advanced cervical cancer is limited by toxicity and resistance.[192–194] Novel approaches are needed. Multicomponent functionalization of 2,5-DBH offers a route to hybrid molecules with enhanced biological potential.[195,196] In this work, Michael adducts of piperazine/2,5-DBH-dithiocarbamate with nitrostyrenes were synthesized (**Scheme 40, 235-240**) via a simple, catalyst-free protocol to generate new apoptotic inducers [197]. In HeLa (HPV 18 positive, IC_{50} 0.989 ± 0.007μM), CaSki (HPV 16 positive, IC_{50} 2.36 ± 0.016 μM), and ViBo (HPV negative, IC_{50} 0.73 ± 0.002 μM) cervical cancer cell lines, all drugs exhibited strong *in vitro* antiproliferative activity with minimal necrotic (cytotoxic) impact. The study's most effective compound (**235**) had greater antiproliferative activity *in vitro* compared to both Paclitaxel and Cisplatin. Compound (**235**) activated caspase-3 to cause apoptosis in all cervical cancer cells without causing necrotic cell death. Furthermore, the LDH cytotoxic assay showed that compound (**235**) had no cytotoxic (necrotic) impact on human cells. But at greater concentrations, compound (**235**) significantly impacted peripheral blood lymphocyte proliferation during the CFSE labeling experiment. It was discovered that the (1*S*,4*S*)-2,5-DBH system performed better in the current design than its piperazine equivalent. These *in vitro* findings undoubtedly portend favourably for more in-depth experiments on mechanistic impacts in the upcoming phase of the study, which will include *in vivo* models.[191]

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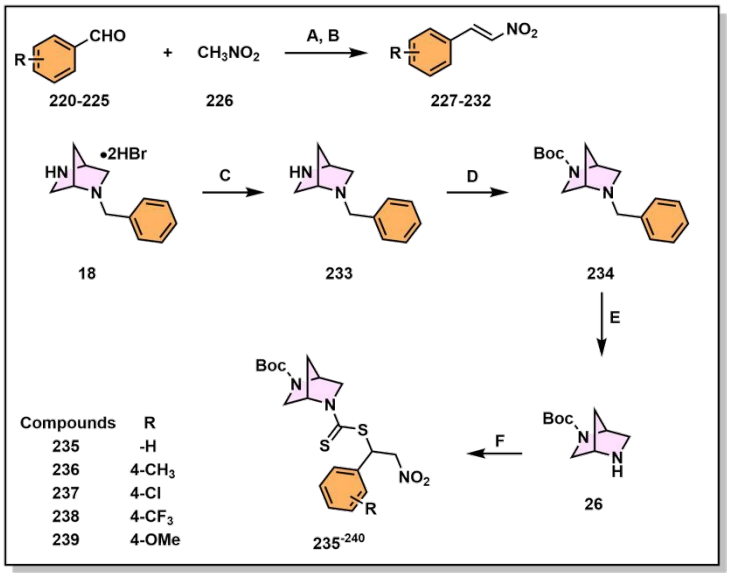

Scheme 40. Synthesis of the hybrid dithiocarbamates. Reactions and conditions: A) aq. NaOH, MeOH; B) HCl, H_2O; C) NaOMe, MeOH, rt; D) Boc_2O, TEA, DCM, 0 °C to rt; E) H_2, $Pd(OH)_2/C$, MeOH; F) CS_2, MeOH, 0 ºC to rt, one-pot; overall yield 50-70%

In 2021, He *et al*. reported the design and development of structurally related analogues of PFI-3 (SRAPs) that enhance the activity of temozolomide in glioblastoma cells by targeting the BRG1 catalytic component of the SWI/SNF complex.[198] The most frequent malignant primary brain tumor in adults, glioblastoma (GBM), is a major contributor to cancer-related morbidity and mortality in the US.[199,200] GBM, or grade IV glioma in the WHO classification, is the most deadly and aggressive kind of brain cancer, comprising around 75% of all instances of glioma. Surgical excision is the main therapeutic option for GBM. Adjuvant chemotherapy with the DNA alkylating drug temozolomide (TMZ) and radiation therapies are also used. Nevertheless, the total median time for a GBM recurrence following conventional treatment is just 7 months, and the general 5-year prognosis is bleak (<10% survival) and has remained mostly constant for decades. Unfortunately, most treated patients eventually experience regrowth of very aggressive brain tumors, often as a result of treatment resistance.[199] The bioactivity of Structurally Related Analogs of PFI-3 (SRAPs) was evaluated *in vitro* by He *et al*. after they were developed and synthesized.[198] The researchers discovered that SRAPs are more effective than PFI-3 at sensitizing GBM cells to TMZ's antiproliferative and cell death-inducing properties *in vitro*. Built on results from cellular thermal shift assays (CETSA), SRAPs bind the BRD of BRG1. Furthermore, they discovered SRAPs that amplified TMZ's inhibitory effect on the development of subcutaneous GBM tumors. The synthesis proceeded as depicted in (**Scheme 41**).

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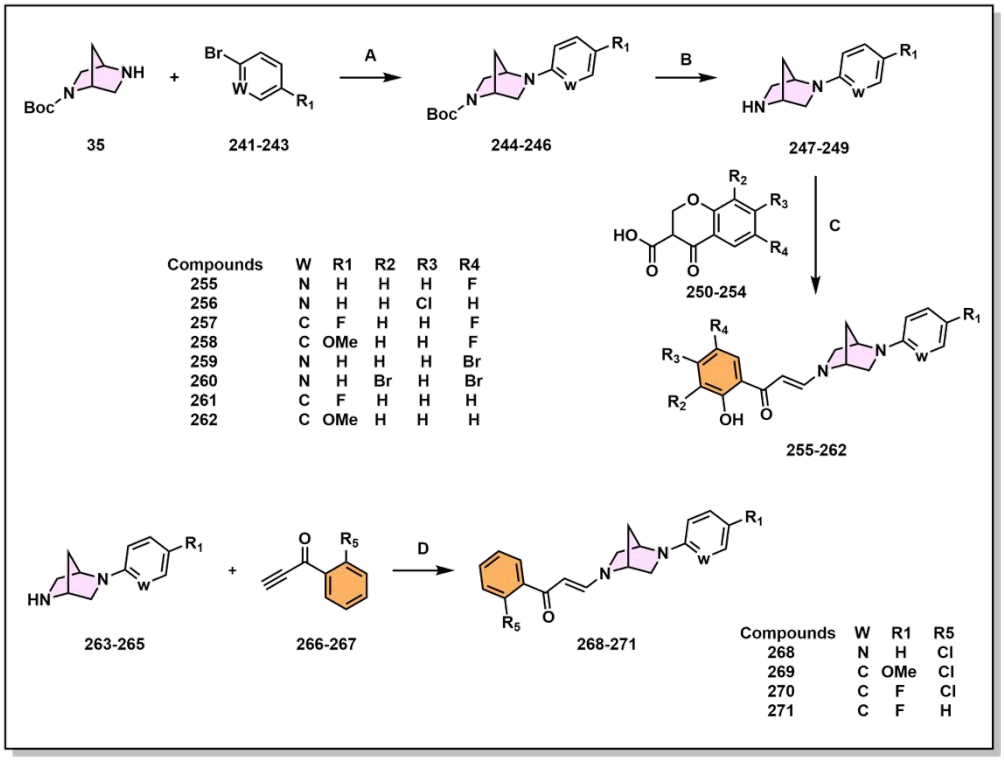
On their own, the novel analogs (**255-262**) and (**268-271**) did not show results in GBM cell killing. SAR studies are depicted in (**Fig. 8**). On the other hand, these analogs work well at making GBM cells more sensitive to TMZ's anFtiproliferative and cell death-inducing properties. Additionally, they discovered that in GBM tumor models, these substances also improve TMZ's anticancer effectiveness. It became clear from this that BRG1 is a target for these recently created substances, which increase TMD's anticancer effects both *in vitro* and *in vivo*.[198]



Scheme 41. Synthesis of structurally related analogues of PFI-3 (SRAPs). Reagents and conditions: A) NaOt-Bu, $Pd(OAc)_2$, BINAP, in toluene, reflux under argon atmosphere, 3–6h, 60-80%; B) 4-N HCl in dioxane, rt under argon atmosphere; C) DIPEA, in ethanol, rt under argon atmosphere, 4–6 h, 55-80%; D) DIPEA, in ethanol, rt under argon atmosphere, 12 h, 30-91%.

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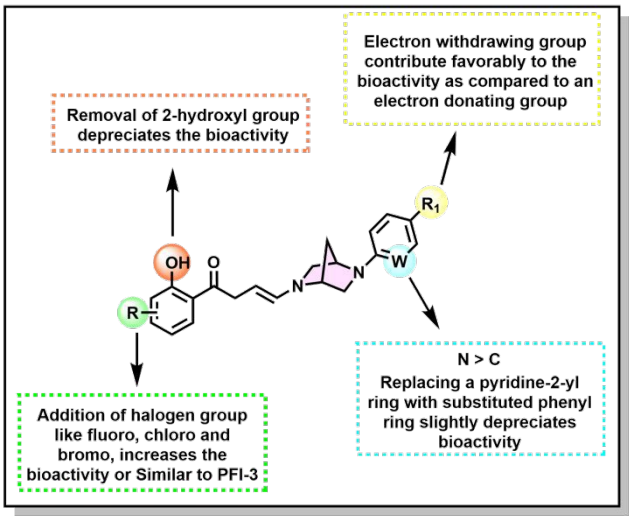

Fig. 8. SAR studies of structurally related analogues coupled 2,5-DBH derivative of PFI-3 (SRAPs).

Zhang *et al*. in 2023 developed a series of methylpropamide derivatives. 2,5-DBH was also a moiety used in this endeavour to furnish a potent, selective androgen receptor antagonist for the treatment of androgenetic alopecia.[201] The most common type of progressive hair loss illness affecting both men and women, androgenetic alopecia (AGA)[202] has a major negative influence on a person's looks and general quality of life.[203] AGA formation and progression are mostly influenced by dermal papilla cells (DPCs) overactivation of the AR signalling pathway.[204] With the serious systemic adverse effects of oral AR antagonists, the concept of creating topical AR antagonists with quick metabolic deactivation capabilities seemed like a good notion.[205–207] The authors developed a fast-metabolizing deactivation AR antagonist for the topical therapy of AGA, due to the promise of AR inhibition as a novel mechanism and the low systemic adverse effects associated with topical use.[208] The target (**276**) was synthesized in a 3-step process illustrated in (**Scheme 42**). The compound had an IC_{50} of 544 nM, antagonizing androgenic receptors proficiently.[201]

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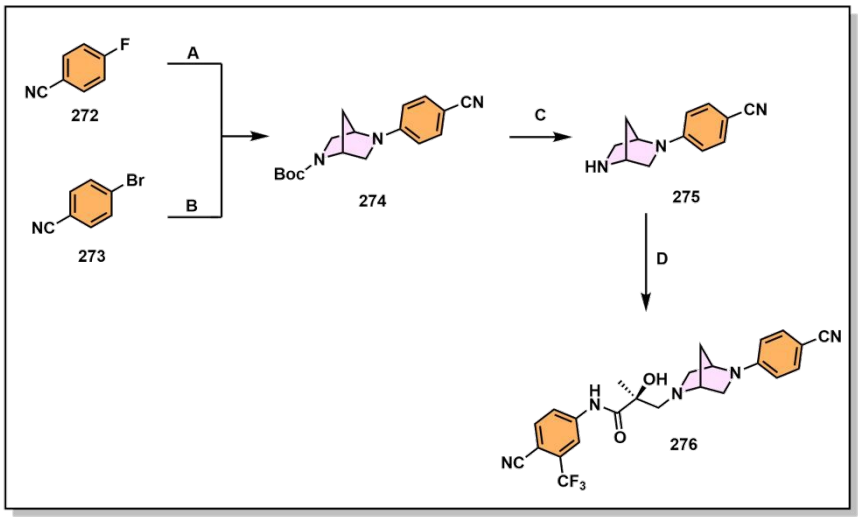

Scheme 42. Synthesis of a series of methylpropamide derivatives.Reagents and conditions: A) related heterocyclic ring, K_2CO_3, DMF, 80 °C, 4 h, 48−93%; B) related heterocyclic ring, $Pd(OAc)_2$, (*t*-Bu)$_3$P, Bu^{t}Na, distilled toluene, N_2, 80 °C, 4 h, or $Pd_2(dba)_3$, BINAP, *t*-BuONa, distilled toluene, N_2, 80 °C, 12 h, or $Pd(OAc)_2$, Xantphos, Cs_2CO_3, anhydrous 1,4-dioxane, N_2, 90 °C, 16 h, 38−81%; C) TFA, DCM, rt, 2 h, 65−95%; D) anhydrous EtOH, N_2, reflux, 4 h, 32−82%.

Foster *et al*. (2024) developed potent, orally bioavailable Spns2 inhibitors.[209] The S1P pathway, already targeted by FDA-approved drugs for ulcerative colitis (UC) and multiple sclerosis (MS), is modulated by S1P1 receptor agonists, which cause desensitization and immunosuppression but also on-target side effects like bradycardia and endothelial barrier disruption.[210–216] Spns2 has emerged as an alternative target.[217] Early inhibitors, including SLF1081851 (IC_{50} 1.93 μM)[218] and SLF80721166 (IC_{50} 1.4 μM)[219], led to the discovery of SLB1122168 (IC_{50} 94 nM)[220], a benzoxazole-based second-generation compound. These inhibitors reduced lymphocyte counts *in vivo*[221] and modulated kidney fibrosis in mice[222], but suffered from poor oral bioavailability or toxicity. Thus, they aimed to create Spns2 inhibitors with better pharmacokinetic and toxicological characteristics. The synthesis of the Spns2 inhibitor series involved multiple steps, beginning with condensation, followed by a Suzuki–Miyaura cross-coupling, one-pot hydroboration–deprotection, and substitution reactions, ultimately affording the target hydrochloride salts of compound (**286**, **Scheme 43**).[209] In mice, inhibitors derived from 2,5-DBH intermediate, when administered orally at a dose of 10 mg/kg, drug exposure reached 1.2 μM at the 4-hour t_{max}. Since this is the first instance of an orally accessible Spns2 inhibitor, the oral bioavailability is significant. In fact, a maximal degree of lymphopenia (about 50%) was noted when lymphocyte counts were taken at 4 hours, which is comparable to what is seen in Spns2 knockout mice. Furthermore, there was no discernible shift in the

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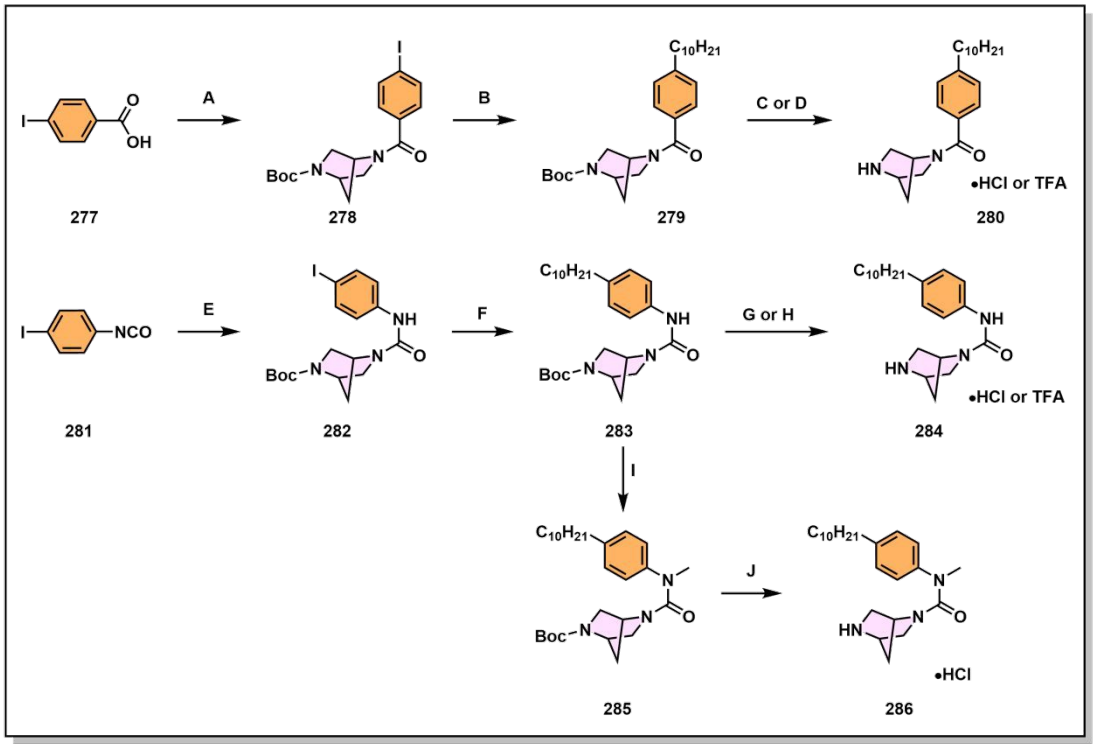
plasma sphingosine-1-phosphate (S1P) level. These metrics point to Spns2's *in vivo* target engagement. All things considered, our research has shown that this inhibitor is a promising *in vivo* chemical probe of Spns2's physiological role, and it offers a framework for further research.[209]



Scheme 43. Synthesis of a series of potent, orally bioavailable Sphingosine-1-Phosphate Transporter (Spns2) inhibitors. Reactions and conditions: A) Mono-*N*-Boc protected diamine, HCTU, DIEA, DCM, rt, 16 h; B) (i) 1-decene, 9-BBN, THF, 66 °C, 2 h; (ii) aryl iodides, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, KOH-aq, THF, 66 °C, 4 h; C) 4-M HCl/dioxane, DCM, rt, 2 h, 65%; D) TFA, DCM, rt, 2 h; E) *N*-Boc protected amino alcohol or mono-*N*-Boc protected diamine, DCM, 0 °C to rt, 16 h; F) (i) 1-decene, 9-BBN, THF, 66 °C, 2 h; (ii) aryl iodides, $PdCl_2(dppf) \cdot CH_2Cl_2$, aqueous KOH, THF, 66 °C, 4 h; G) 4-M HCl/dioxane, DCM, rt, 2 h; H) TFA, DCM, rt, 2 h; I) (i) NaH, THF, 0 °C, 0.5 h; (ii) MeI, THF, 0 °C to rt, 16h; J) 4-M HCl/dioxane, DCM, rt, 2 h, 67%.

4.7 Synthesis and Biological Profile of 2,5-diazabicyclo[2.2.1]heptane with Miscellaneous moieties.

Shchekotikhin *et al.* developed a series of novel 3-aminomethyl-4,11-dihydroxynaphtho[2,3-f]indole-5,10-diones incorporating cyclic diamines in their side chains (Scheme 44). Among these, the 2,5-DBH-based derivative **(290)** exhibited

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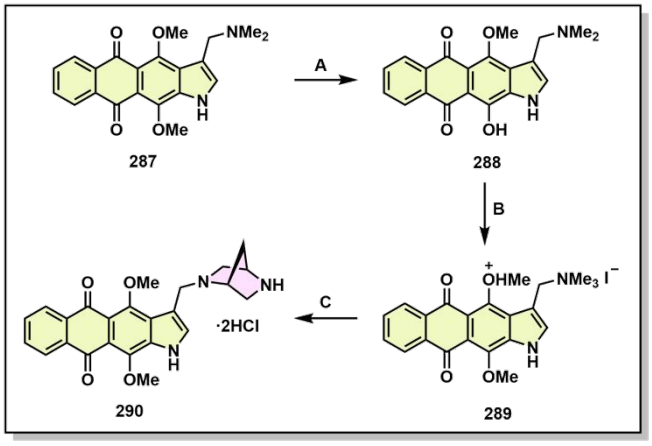
pronounced cytotoxic activity across a broad spectrum of mammalian tumor cell lines, with potency observed in the submicromolar to low micromolar range. These results underscore the promise of such scaffolds as potential leads for anticancer drug discovery. The antiproliferative analysis further revealed that compound (**290**) induced strong antiproliferative effects against HCT116 and HCT116$_P$55ko human colorectal carcinoma cell lines, with IC_{50} values of 6.4 μM and 6.9 μM, respectively, highlighting its efficiency in suppressing both wild-type and drug-resistant cancer cells.[223]



Scheme 44. Synthesis of 3-aminomethylnaphtho[2,3-f]indole-5,10-dione containing DBH. Reagents and conditions: A: HCl in glacial acetic acid, rt, 24 h, 78%; B: methyl iodide, chloroform, reflux, 1 h; C: Boc-2,5-DBH, HCl in glacial acetic acid, 24 h, 61%.

Recent advancements in the treatment of lung cancer, particularly non-small cell lung cancer (NSCLC), have been significantly influenced by the introduction of molecular targeted therapy (MTT). This approach focuses on specific genetic alterations, such as chromosomal translocations, point mutations, and gene amplifications, allowing for the identification of genotype-specific patient subsets and optimizing clinical outcomes. One important target in this context is the anaplastic lymphoma kinase (ALK), which is present in 3-5% of NSCLC cases, typically involving a fusion with the EML4 gene.[224] Among the second-generation ALK inhibitors, Ceritinib and Alectinib represent distinct chemotypes with unique structural features. Jiang *et al*. designed four series of tetracyclic benzo[*b*]carbazolone compounds with increased molecular flexibility and more rotatable bonds (**Scheme 45**). This was achieved by adding a linker to the C8 side chain or by modifying the ketone ring structure based on Alectinib.

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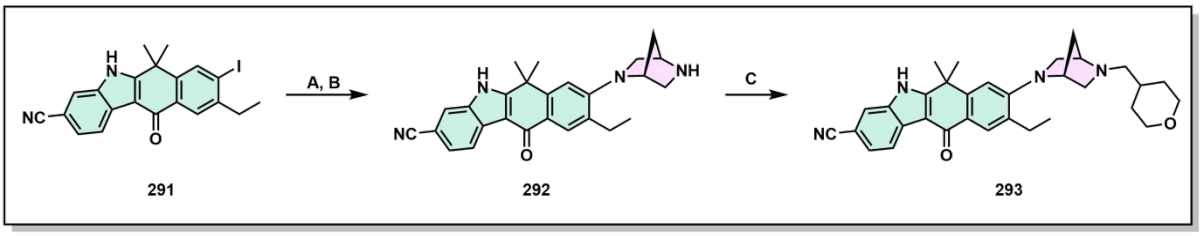
The key compound (**293**) was obtained in a 54% yield and demonstrated potent ALK inhibition with an IC_{50} of 6.6 nM.[225]



Scheme 45. Synthesis of an ALK inhibitor containing DBH. Reagents and conditions: A) $Pd_2(dha)_3$, S-Phos, NaHMDS (2 M in THF), dioxane, 60 °C; B) TFA, DCM, rt, 49%; C) K_2CO_3, DIPEA, KI, 55 °C to 80 °C in DMF, 54%.

The androgen receptor (AR), part of the nuclear hormone receptor superfamily, plays a vital role in both the development of the prostate gland and the maintenance of male secondary sexual characteristics.[226] Recently, a novel therapeutic strategy known as induced target protein degradation (TPD) has gained significant attention. This approach leverages the proteolysis-targeting chimera (PROTAC) technology platform, which is designed to degrade specific proteins within cells.[227] PROTACs are heterobifunctional small molecules composed of two distinct ligands: one that binds to the protein of interest (POI) and another that targets an E3 ligase or an E3 ligase complex.[228] These two components are connected by a linker, allowing for the formation of a complex that facilitates protein degradation. Han *et al*. reported the design, synthesis, and characterization of a new class of PROTACs specifically targeting the androgen receptor, where 2,5-DBH acts as a linker between both ligands (**Scheme 46**). Notably, the PROTAC featuring a 2,5-DBH (compound **305**) emerged as a highly effective AR degrader. It demonstrated the ability to reduce AR protein levels by more than 90% at a concentration of 10 nM and achieved reductions exceeding 95% at both 100 nM and 1000 nM concentrations. Moreover, the degradation of AR protein in LNCaP and VCaP prostate cancer cell lines resulted in substantial suppression of AR-regulated genes, thereby inhibiting the growth of cancer cells. This finding underscores the potential of utilizing PROTAC technology as a powerful therapeutic strategy for targeting androgen receptor-related pathways in prostate cancer treatment.[229]

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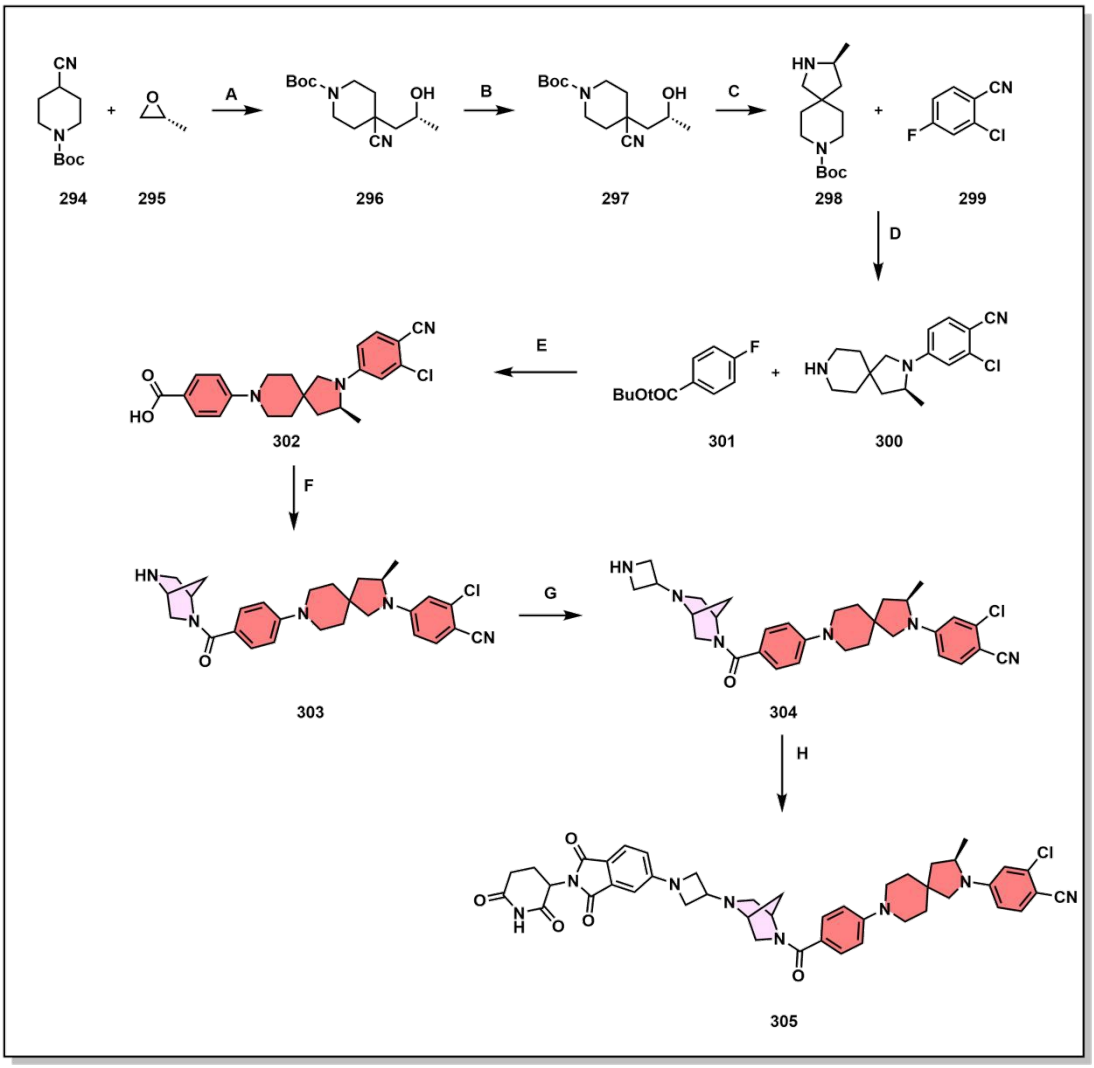

Scheme 46. Synthesis of PROTAC containing 2,5-DBH. Reagents and conditions: A) LDA, THF,−78 to 0°C; B) MsCl, TEA, DMAP, DCM, 0°C; C) LiAlH4, THF, rt; D) DIPEA, DMSO, 100°C then TFA, DCM, rt; E) DIPEA, DMSO, 100°C; then TFA, DCM, rt; F) HATU, DIPEA, DMF, rt then TFA, DCM, rt; G) $NaBH(OAc)_3$, AcOH, DCE, rt. then TFA, DCM, rt; H) DIPEA, DMSO, 100°C; overall yield 80%

Trometer *et al*. conducted a study to identify potent anti-*T. cruzi* derivatives derived from a library of 3-benzylmenadiones. They developed a synthetic approach to create a collection of 3-(4-monoamino)benzylmenadione derivatives through reductive amination, ultimately leading to the formation of 2,5-DBH-linked menadione derivatives illustrated in (**Scheme 47**). Among these derivatives, the most effective was identified as compound (**310**), which demonstrated an impressive IC_{50} value of 23.4 nM against *T. cruzi*.[230]

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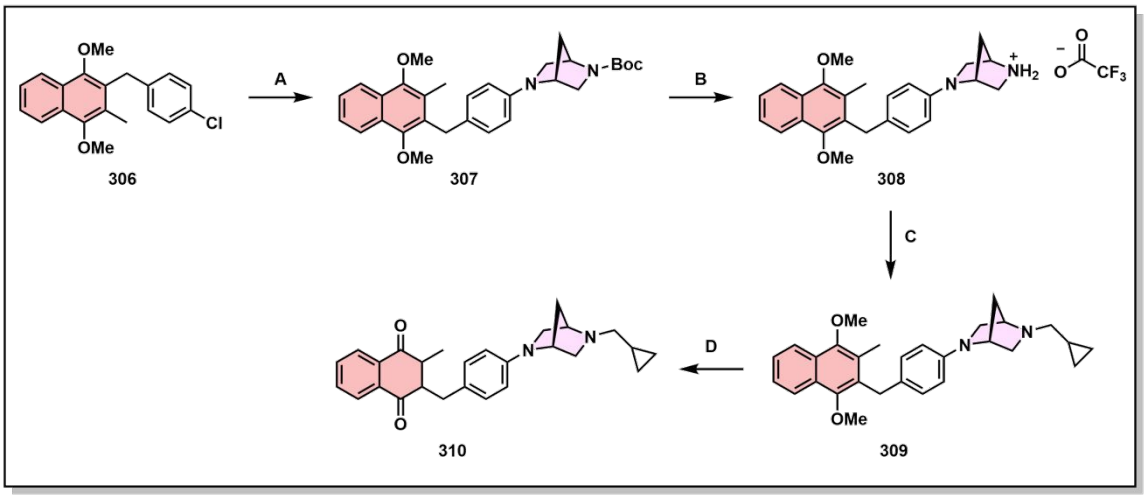

Scheme 47. Synthesis of dihydronaphthalene-1,4-dione derivative containing 2,5-DBH. Reagents and conditions: A) Diazacycle, $Pd(dba)_2$, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, ^tBuOK, toluene, reflux, 2.5 h, 49%; B) TFA, DCM, rt, 1 h, quantitative yield; C) Aldehyde, $NaBH(OAc)_3$, NEt_3, DCE, rt, 16−20 h, 70%; D) BCl_3, TBAI, DCM, −78 °C to rt, 16 h, 76%.

Tuberculosis (TB) remains one of the deadliest chronic infectious diseases globally, primarily caused by the bacterium *Mycobacterium tuberculosis* (MTB). Researchers have identified several nitrofuran derivatives that demonstrate promising potential as anti-TB agents, leading to extensive investigation in this area. In a significant study, Wang *et al*. focused on the synthesis of nitrofuranyl methyl *N*-heterocycles, identifying them as effective anti-TB compounds (**Scheme 48**). Among the newly developed derivatives, one notable compound, designated as compound (**312**), based on the 2,5-DBH structure, exhibited impressive minimum inhibitory concentrations (MIC) of 6.54 μg/ml and 5.94 μg/ml against multidrug-resistant strains of *M*. *tuberculosis*, specifically MDR-MTB16833 and MDR-MTB16995, respectively. This innovative approach highlights the potential of these nitrofuran derivatives in the ongoing fight against tuberculosis.[231]

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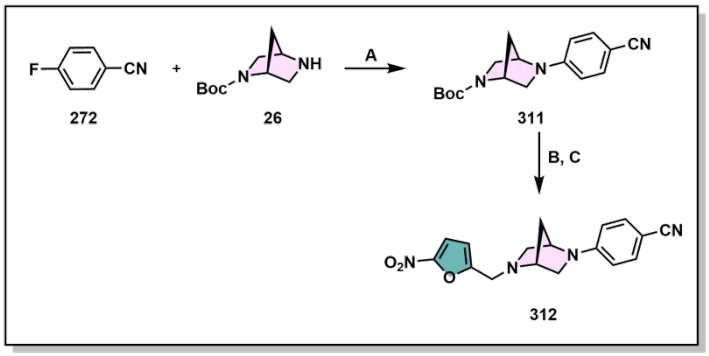

Scheme 48. Synthesis of nitrofuranyl methyl linked with 2,5-DBH. Reagents and Conditions: A) K_2CO_3, DMSO, 80 °C, 4 h, 62%; B) trifluoroacetic acid, DCM, rt, 3 h; C) $Na(OAc)_3BH$, AcOH, DCM, rt, 12 h, 32%.

5. Conclusion and Future Perspective.

This review aims to provide essential support to medicinal chemists in their search for new *N*-heterocyclic compounds. The bicyclic nucleus of 2,5-DBH has emerged as a valuable structural motif in the development of *N*-heterocyclic compounds. 2,5-DBH serves as a highly stable and rigid bicyclic amine structure, making it particularly valuable in medicinal chemistry for its conformational and electronic properties. Various synthetic strategies, such as epimerization, lactamization, and the tandem Strecker reaction–intramolecular nucleophilic cyclization (STRINC), have been successfully developed to produce orthogonally protected derivatives and non-protected forms of this bicyclic structure. These approaches not only allow for precise stereochemical control but also offer flexibility in subsequent modifications, enhancing the versatility of 2,5-DBH as a building block in advanced organic synthesis. The bicyclic framework of 2,5-DBH provides restricted rotation, which enhances receptor binding affinity and specificity in bioactive molecules. The nitrogen atoms of the 2,5-DBH scaffold enable compatibility with electrophilic centers, allowing for the generation of stable linkages with various heterocycles via several reactions, e.g., nucleophilic substitution and coupling reactions, which facilitate diverse modifications that expand its utility in synthetic pathways. The derivatives of 2,5-DBH represent a diverse class of compounds with promising bioactivity across various therapeutic fields. These compounds have shown potential as anticancer agents, antimicrobials, antiparasitic, and antivirals. They also hold promise in addressing neurodegenerative diseases, displaying notable neuroprotective properties, as well as in treating cardiovascular conditions due to their vasodilatory effects. Altogether, the broad and

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multifaceted bioactivity of 2,5-DBH derivatives underscores their versatility and therapeutic opportunities.

6. Author's Perspective

There has been a sustained and growing interest in the design, synthesis, and biological evaluation of 2,5-DBH derivatives in recent years, leading to the development of effective compounds targeting various therapeutic areas. While the 2,5-DBH framework can be utilized as a core structure, linker, or substituent, most studies have predominantly focused on its role as a substituent. Several 2,5-DBH–containing molecules, particularly when functionalized with various heterocycles, demonstrated nanomolar potency against their respective targets. As a core scaffold, compound (**160**) incorporating 2,5-DBH with triazine exhibited LFA-1 inhibition, while compound (**163**) linked with imidazopyrazine acted as a SYK inhibitor for solid tumors. Compounds (**255–271**), bearing phenyl ring substitutions, demonstrated activity against glioblastoma. As a linker, 2,5-DBH conferred activity against 5-HT7Rs when combined with aryl sulphonamide systems and phenols (compounds **203–206**). Additionally, compound (**276**) displayed potential for androgenetic alopecia treatment, compound (**293**), a 2,5-DBH–linked benzo[*b*]carbazolone, showed efficacy against NSCLC, and compound (**305**), a PROTAC incorporating 2,5-DBH, proved effective as an androgen receptor degrader.

When employed as a substituent, notable examples include compound (**64**), a 2,5-DBH–pyridine hybrid with remarkable potency against hepatocellular carcinoma, and compound (**69**), which displayed activity in AIDS when functionalized with piperidine. Compound (**91**), incorporating multiple monoaza substituents, was effective against mixed lineage leukemia, while compound (**100**), a quinazolinone-conjugated derivative, demonstrated potent PI3Kδ inhibition. Compound (**104**), containing benzimidazole, exhibited DGAT1 inhibition, whereas compound (**136**) with multiple diaza heterocycles displayed activity against acute myeloid leukemia. Similarly, compound (**143**) showed potency against amyotrophic lateral sclerosis, compound (**146**) with pyrimidine inhibited BMPR2, and compound (**154**), containing pyrimidine and indazole, exhibited strong anticancer activity against breast cancer. Further examples include compound (**175**), which demonstrated anti-inflammatory effects

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when linked to thiazolo[4,5-b]pyridines, and compound (**310**), a 2,5-DBH–menadione conjugate with antiparasitic activity.

Integrating 2,5-DBH into drug design not only enhances the therapeutic potential of these compounds but also facilitates the fine-tuning of pharmacokinetic properties. Despite the progress made, there remains significant untapped potential for 2,5-DBH in medicinal chemistry and related fields. The ease of chemical modification and the broad spectrum of biological applications associated with 2,5-DBH derivatives suggest that this scaffold offers a wealth of opportunities for future research. We hope that the insights presented in this review will inspire researchers to further explore the diversity and potential of this promising scaffold.

7. Acknowledgment

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8. CRediT authorship contribution statement

Pranav Kumar Ambast: Investigation, Writing – original draft, Writing – review & editing. **Saumya Kapoor:** Writing – original draft, Writing – review & editing. **Rudradip Das:** Writing – original draft, Writing – review & editing. **Deep Rohan Chatterjee:** Writing – review & editing. **Amit Shard:** Supervision, Funding acquisition, Conceptualization, Writing – review & editing.

9. Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work report.

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10. Declaration of generative AI use

Generative AI and AI-assisted technologies were only used in the writing process to improve the readability and language of the manuscript

11. Data availability statements

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

12. Abbreviations used:

AIDS: acquired immunodeficiency syndrome; **AKR**: aldo-keto reductase; **ALL**: lymphoblastic leukemia; **ALS**: amyotrophic Lateral Sclerosis ; **AML**: acute myeloid leukemia; **AR**: androgen receptor; **BET**: bromodomain and extraterminal domain; **BMPR2**: bone morphogenetic protein receptor type II kinase; **BMPs**: bone morphogenetic proteins; **BTK**: bruton's Tyrosine Kinase; **BTZs**: benzothiazinones; **CCR5**: chemokine receptor 5; **CDK**: cyclin-Dependent Kinase; **CRDAs**: conformationally restricted diamines; **Cy3**: cyanine3; **DBHs**: diazabicycloheptanes; **dCTPase**: deoxyribonucleotide triphosphate pyrophosphatas; **DEAD**: diethyl azodicarboxylate; **DEL**: DNA-encoded library technology; **DGAT1**: diacylglycerol acyltransferase 1; **DIPEA**: *N*, *N*-Diisopropylethylamine; **DIPG**: Diffuse intrinsic pontine glioma, **DLK**: dual Leucine Zipper Kinase; **DprE1**: D-ribose 2'-epimerase; **EDG**: electron-donating groups; **EGFR**: Epidermal growth factor receptor; **ELT**: encoded library technology; **EWG**: electron-withdrawing groups; **FAAH**: fatty acid amide hydrolase; **FBDD**: fragment-based drug design; **FLT3**: Fms-like tyrosine kinase 3; **FLAP**: 5-lipoxygenase-activating protein; **FOP**: fibrodysplasia ossificans progressiva **FTO**: fat mass and obesity-associated protein; **FtsZ**: filamenting temperature-sensitive mutant Z; **HAART**: highly active antiretroviral therapy; **HAT**: Human African trypanosomiasis; **HATU**: hexafluorophosphate azabenzotriazole tetramethyl uranium; **HIV**: human immunodeficiency virus; **HOXA**: homeobox A cluster; **ICAM-1**: intercellular adhesion molecule-1; **ILDs**: idiopathic lung disorders; **IPF**: idiopathic pulmonary fibrosis; **KHMDS**: potassium bis(trimethylsilyl)amide; **LAD I**: leukocyte adhesion deficiency type I; **LFA-1**: lymphocyte function-associated antigen-1; **LLE**: lipophilic ligand efficiency; **LPA**: lysophosphatidic acid; **LPA2**: lysophosphatidic acid receptor 2; **LSD 1**: lysine-specific demethylase 1; **LTA4H**: leukotriene A4 hydrolase; **LZK**: leucine Zipper-Bearing Kinase; **MDR-MTB**:

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multidrug-resistant tuberculosis; **MEIS1**: meis Homeobox 1; **MLL1**: mixed lineage leukemia; **MTT**: molecular targeted therapy; **NSCLC**: non-small cell lung cancer; **PAK1**: p21-activated kinase 1; **PI3K**: Phosphoinositide 3-kinases; **PMA**: phorbol myristate acetate; **PROTAC**: proteolysis-targeting chimera; **SBDD**: structure-based drug design; **SN_{Ar}**: nucleophilic aromatic substitution reaction; **Spns2**: Sphingosine-1-PhosphateTransporter; **STRINC**: strecker reaction–intramolecular nucleophilic cyclization; **SYK**: spleen tyrosine kinase; **TEA**- triethylamine; **TEC**: tyrosine kinase expressed in hepatocellular carcinoma; **TFA**: trifluoroacetic acid; **TGF-β**: transforming growth factor-beta; **TG2**: transglutaminase 2; **TPD**: target protein degradation; **T3P**: 2,4,6-tripropyltrioxatriphosphinane 2,4,6-trioxide; **UIP**: idiopathic usual interstitial pneumonia; **XDR-MT**: Extensively drug-resistant tuberculosis; **2,5-DBH**: 2,5-diazabicyclo[2.2.1]heptane; **5-LO**: 5-lipoxygenase

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Data availability statements

No primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

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