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5,6,7,8-TETRAHYDROPYRIDO[3,4-*d*]PYRIMIDINES: A RECENT PERSPECTIVE ON SYNTHESIS AND BIOACTIVITY

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ABSTRACT

Adagrasib, a selective KRAS G12C inhibitor, stands out with its favorable pharmacokinetic profile, including a prolonged half-life (around 23 hours) compared to Sotorasib. The synthetic approach for Adagrasib involves utilizing the 5,6,7,8-tetrahydro pyrido[3,4-*d*]pyrimidine (**1**) scaffold. The selective functionalization of a 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine nucleus through three different types of reactions: Suzuki coupling at the C-2 position, nucleophilic substitution at the C-4 position, and electrophilic substitution at the C-7 position, enables the generation of diverse molecules with latent therapeutic applications. Research continues to explore its potential in combination therapies and other tumor types, highlighting the importance of the 5,6,7,8-tetrahydro pyrido[3,4-*d*]pyrimidine scaffold. These synthetic advancements, including the demonstration of promising biological activity, are encouraging and driving the development for synthesis of new drugs. Hence, recent progress in the preparation and pharmacological evaluation of **1** covers the literature up to September 2024. This review is arranged chronologically and according to biological activity, highlighting key advancements in the field.

Keywords: Tetrahydropyrido[3,4-*d*]pyrimidine, Suzuki coupling, Adagrasib, Synthesis, Activity.

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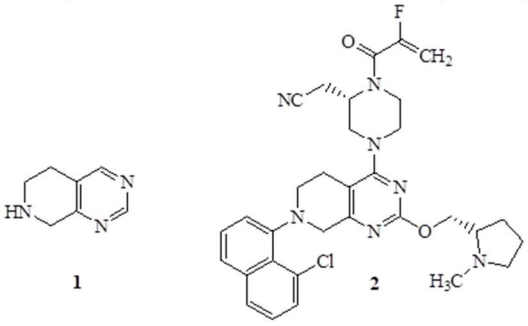
INTRODUCTION

The compound **1** is an organic heterocyclic formed by the fusion of pyrimidine with a piperidine ring and exhibits affinity and selectivity towards various biological targets. For example, Adagrasib (**2)** is used to treat lung cancer and is also a selective covalent inhibitor of $KRAS^{G12C}$ mutant protein with a better half-life of 23 hr as Sotorasib has 5 hr. Further, Adagrasib is proven to penetrate effectively the CNS was attributed to its inhibition of P-glycoprotein-mediated efflux for plausible effective clinical outcomes in the treatment of $KRAS^{G12C}$ - mutated NSCLC tumors.[1] Various compound **1** derivatives demonstrated numerous therapeutic activities including anti HIV[2], alpha-1 adrenoceptor antagonist[3], 5-HT2A antagonists[4], antiproliferatives[5,6], mTOR inhibitors[7], inhibitors of Bcl-2[8], inhibitors of ERK2[9,10], VEGFR-2 inhibitors[11], AAA+ ATPase p97 inhibitors[12], P2X7 antagonists[13], irreversible covalent inhibitors of KRAS-G12C`[14], anticancers[15,16,17], GPR119 and DPP-4 modulators[18], Axl inhibitors[19], anti-TB[20], anti-leukemic agents[21] and antimicrobial.[22] The commercial process has been developed for the marketed anti-lung cancer drug-Adagrasib (**2**).[23,24] In this context, the reported synthesis and importance of these tetrahydropyridopyrimidines are reviewed and presented as a prelude to our efforts to develop a 'drug candidate' from this class of heterocycles, and cover the literature up to September 2024.



1 2

Still coupling of tetrahydropyrido[3,4-*d*]pyrimidinyl chlorides **3** with 3-(tributylstannyl)pyridine gave compound **4.** Deprotection of **4** followed by coupling with 2-oxoacetic acid derivative **5** in the presence of

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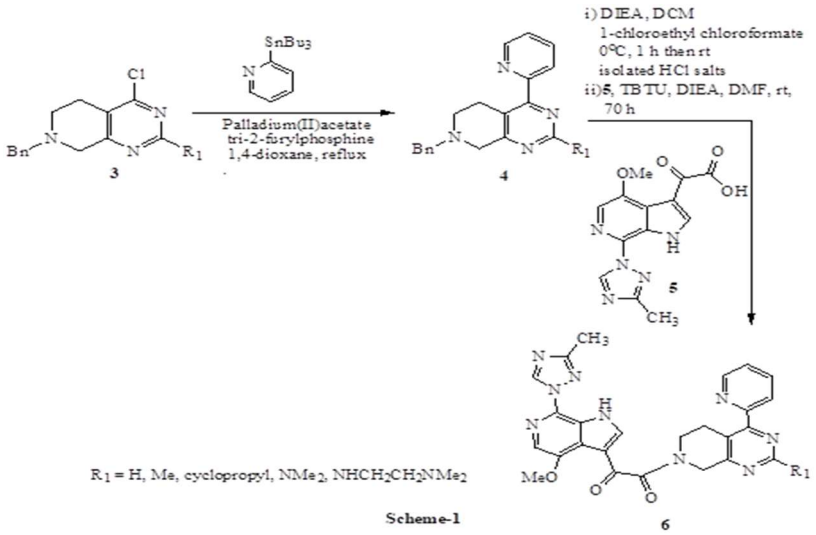
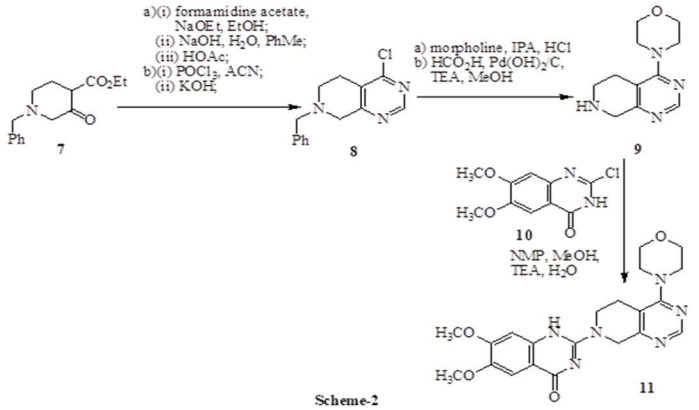
TBTU gives tetrahydropyrido[3,4-d]pyrimidines **6**. These compounds **6** were demonstrated to have activity at subnanomolar concentrations in HIV-1 infections (Scheme-1).[2]



Scheme-1

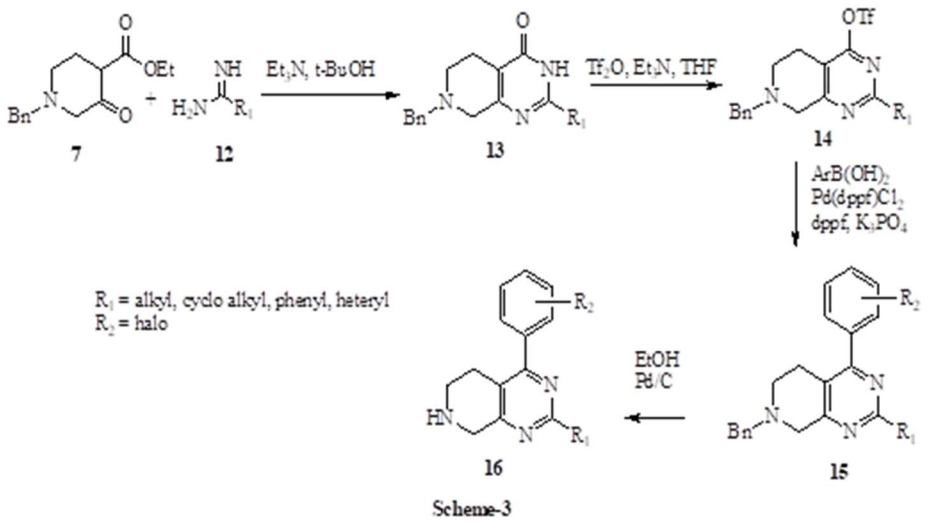
Connolly *et. al* developed the production of tetrahydropyrido[3,4-*d*] pyrimidines **11** by the reaction of keto ester **7** and formamide acetate then chlorination with $POCl_3$ to give compound **8**, amination with morpholine to compound **9** followed by reaction with 2-chloro-6,7-dimethoxyquinazolin-4(3*H*)-one (**10**) at pilot scale level employing 2 level pilot plant process to meet the larger quantities for pre-clinical studies. The 2nd pilot plant operation allowed them to improve the process at the front-end and product quality over the laboratory scale of these α-1 Adrenoceptor antagonist (Scheme-2).[3]



Scheme-2

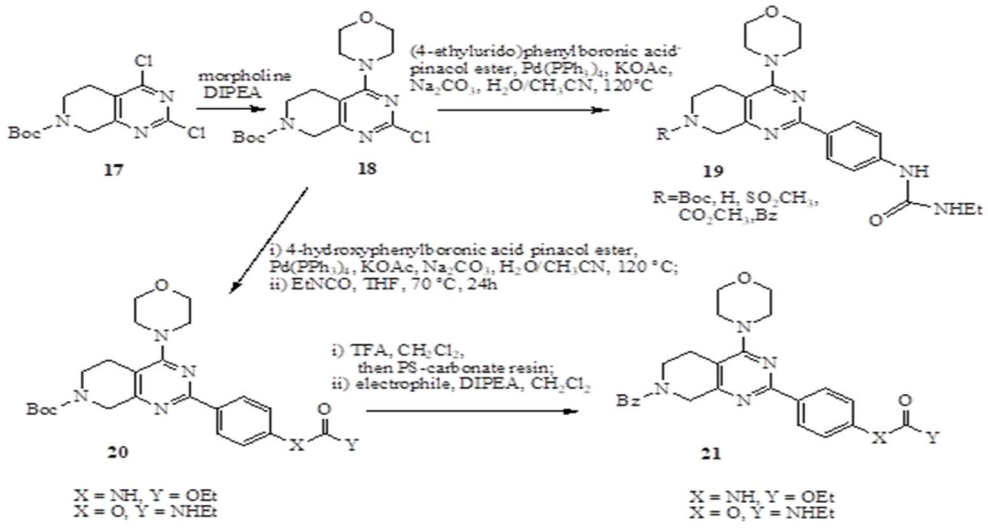
The tetrahydropyrido[3,4-*d*]pyrimidines **16** were derived from β-ketoesters **7.** Condensation of **7** with amidines **12** in refluxing t-BuOH in the presence of TEA gave compound **13**, treatment with Tf_2O and TEA in MDC yielded **14**, reaction with aryl boronic acids containing tripotassium phosphate, dppf, and $Pd(dppf)Cl_2$ in dioxane at 100°C yielded **15**, and debenzylation afforded compound **16**. Few compounds were demonstrated as 5-HT2A antagonists. Neurotransmitter serotonin 5-HT_{2A} subtype, in coupling with G-protein, acts as a ligand-gated ion channel and is known for its association with disturbances in slow wave sleep quality and quantity. 5-HT_{2A} Antagonist(s), amine pyrimidine(s) are being used in the therapy of neuropsychiatric disorders of sleep with diverse side effects owing to the high-level homology of the 5-HT_{2A} with the other thirteen receptors. This study identified subtype-specific alkyl pyrimidine analogues, of which a few of them exhibited selective affinity to 5HT_{2A} with 0.4 to 0.8 Nm (Scheme-3).[4]

Tetrahydropyrido[3,4-*d*]pyrimidines **19**, **20, 21** were prepared from dichloro compound **17** through substitution at C_4 chloride to compound **18,** then reaction at C_2 by Suzuki coupling. These title compounds exhibit single-agent antiproliferative activity. These compounds were found to suppress mTORC1 and mTORC2 *in vitro* and *in vivo*.



Scheme-3

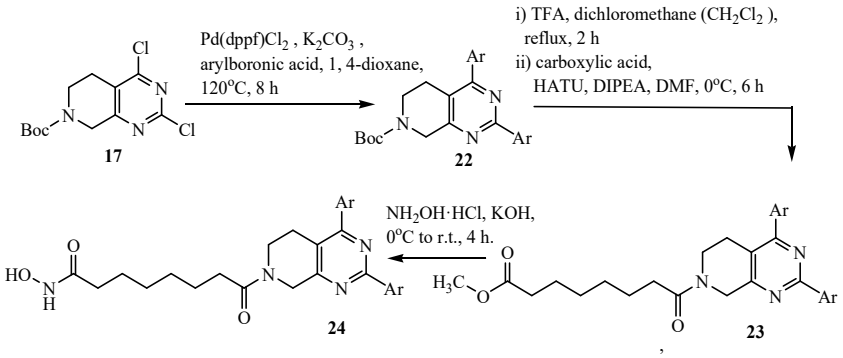
However, these compounds failed to induce comparable hyperphosphorylation of Akt with that of rapamycin. Further efficacy of translation of these compounds was lower than expected in the PC3 xenograft model. However, further refinement of these compounds with reduced inhibitory effect on CYP 3A4 could be introduced into clinical trials for effort to understand any drawbacks (Scheme-4).[5]



Scheme-4

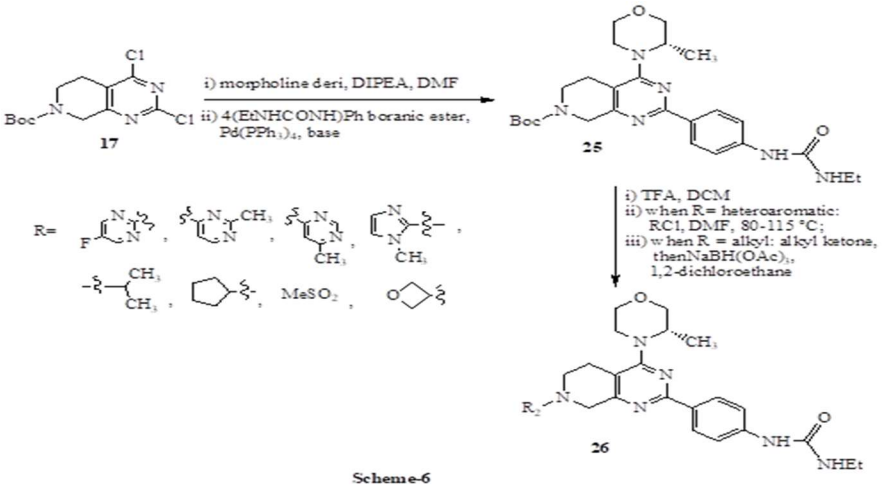
The Suzuki reaction of **17** and two equivalent of arylboronic acids yielded 2, 4-diaryl-7-(tert-butyloxycarbonyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidines **22**. Boc deprotection with TFA/MDC and following reaction with suberic acid monomethyl ester in the presence of HATU, gave ester **23**. Then, **23** were converted to tetrahydropyrido[3,4-*d*]-pyrimidines **24** using hydroxylamine solution in basic medium. All these compounds are potent antiproliferatives at a nM level and 16~49-fold discriminating than HDAC1. These have potent anti-proliferative activity in 59 cancer cell lines belonging to diverse cancers. But for three compounds, all the cell lines exhibited more than 80% inhibition at 10 µM concentrations. Most potent compound **24** exhibited a dose-dependent increase (Scheme-5).[6]

Pei *et al.* have synthesised mTOR inhibitors, tetrahydropyrido[3,4-*d*]pyrimidine derivatives **26**, from compound **17** by reacting with methylmorpholine deri. and aryl boranic acid ester followed by deprotection and heterylation/alkylation of the resulting intermediate **25**. The compound **26** effectively inhibited mTORC1 as well as cytochrome P450 (CYP3A4) in a dose-dependent manner. When orally administered to the mice, MCF7-neo/Her2 tumor xenograft showed maximum tolerance with favorable free plasma clearance (Scheme-6).[7]



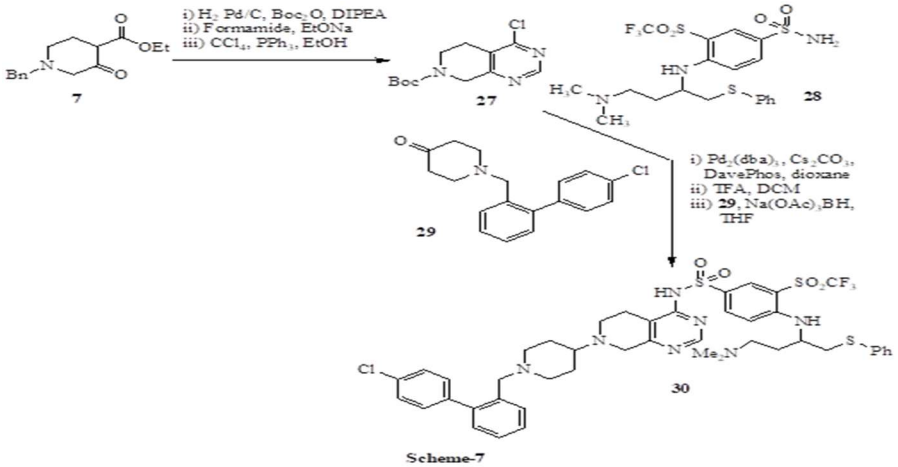
Ar=C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, furan-3-yl, thiophen-3-yl, 3-$CH_3OC_6H_4$, thiophen-2-yl, 4-$CF_3C_6H_4$

Scheme-5



Scheme-6

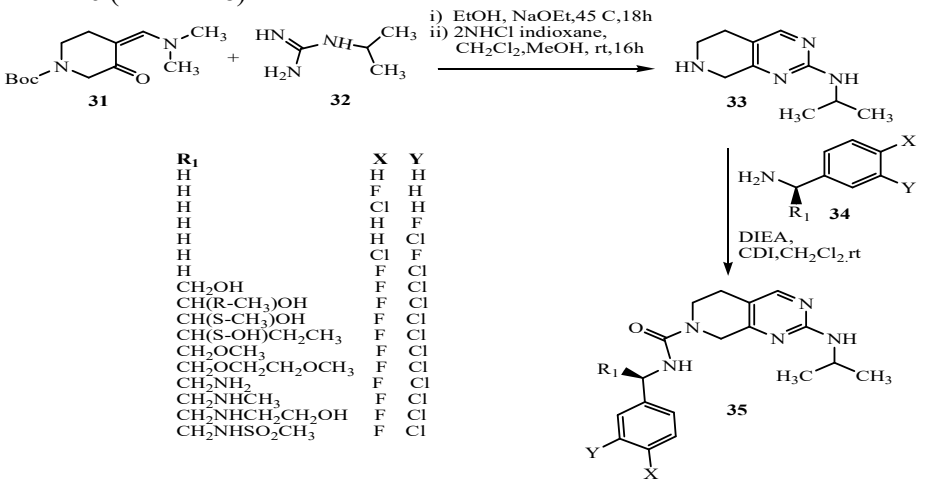
The chloro compound **27**, which was obtained from compound **7,** was reacted with aryl sulphonamide **28,** deprotection, then reaction with piperidinone derivative **29** to form 5,6,7,8-tetrahydropyrido [3,4-*d*]pyrimidine **30**. The **30** was found effective as a Bcl-2 antagonist, also inhibiting Bcl-xL with an IC_{50} of 24 nM, plausibly contributing to the programmed cell death. Further, this molecule exhibited improved solubility, addressing the major concern for the oral absorption (Scheme-7).[8]



Scheme-7

Blake *et al.,* developed Erk2-specific inhibitors by employing the synthesis of a combinatorial library, HTS, and SBDD. Synthesized the bioactive molecules from the methyleneoxopiperidine derivative **31**. The

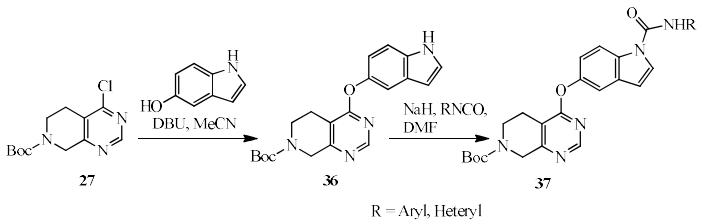
compound **31** and isopropyl guanidine (**32**) were reacted in the presence of sodium methoxide and then deprotected with 2N HCl to find the corresponding diamine **33**. The **33** and benzyl amine derivatives **34** were coupled with CDI in DCM in the presence of DIEA to afford the final compounds **35**. The tetrahydropyridopyrimidine(s) **35** showed potent and selective Erk2 inhibitor, by drastically reducing phospho-RSK activity and HepG2 cell proliferation as well as inhibition of tumor establishment in xenografts of HCT116 (Scheme-8).[9]



R_1	X	Y
H	H	H
H	F	H
H	Cl	H
H	H	F
H	H	Cl
H	Cl	F
H	F	Cl
CH_2OH	F	Cl
$CH(R\text{-}CH_3)OH$	F	Cl
$CH(S\text{-}CH_3)OH$	F	Cl
$CH(S\text{-}OH)CH_2CH_3$	F	Cl
CH_2OCH_3	F	Cl
$CH_2OCH_2CH_2OCH_3$	F	Cl
CH_2NH_2	F	Cl
CH_2NHCH_3	F	Cl
$CH_2NHCH_2CH_2OH$	F	Cl
$CH_2NHSO_2CH_3$	F	Cl

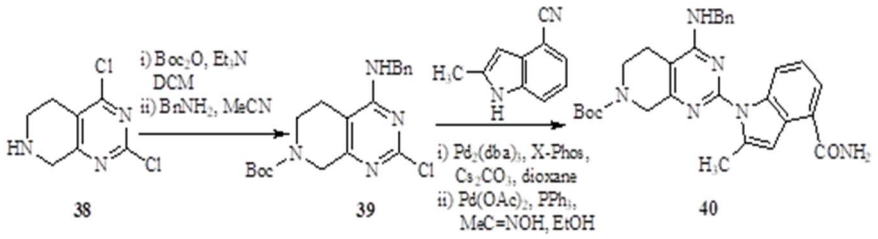
Scheme-8

Meredith *et al*., have synthesized VEGFR-2 inhibitors, 4-((1-(substituted carbamoyl)-1*H*-indol-5-yl)oxy)-7-tertiarybutyloxycarbonyl-5,6-dihydropyrido[3,4-*d*]pyrimidines **37** by reacting compound 2**7** with 1*H*-indol-5-ol to yield ether derivative **36,** followed by reaction with isocyanate derivatives. AMD is known to produce vision loss owing to pathology in the macula. The therapies of intravitreal injections are effective in only 60% patients. The requirement of a monthly dose causes financial burden to the patients as well as vision loss due to infections and several other reasons. Compounds developed in this study assayed biochemically for their selectivity for the VEGFR-2 receptor tyrosine kinase panel inhibitors, consisting of 62 kinases. The selected compounds were further evaluated cellular model BaF3-Tel- KDR cells engineered for the constitutive requirement of VEGFR-2 kinase domain. Subsequently, compounds were assayed using mouse CNV and rat CNV models. A couple of compounds exhibited high water solubility, oral bioavailability, as well as were highly suitable for local administration, providing higher ocular exposure with minimum side effects (Scheme-9).[11]



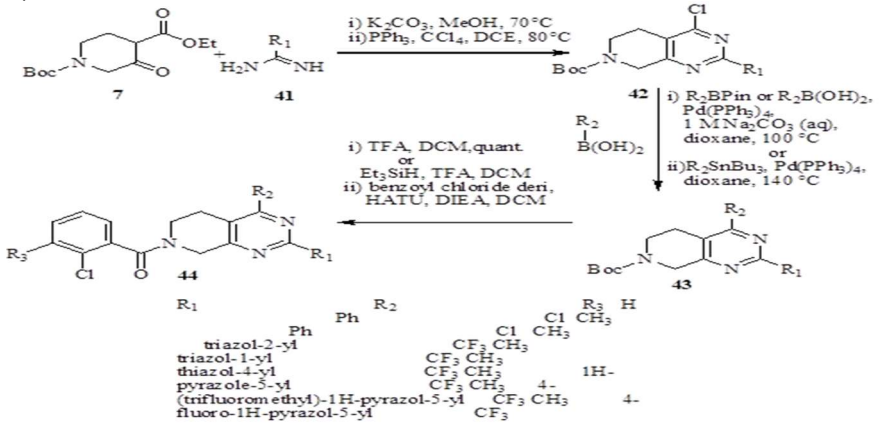
Scheme-9

Amination of **38** with benzyl amine to compound **39** and C-N cross-coupling reaction with 4-cyano-2-methyl-1*H*-indole yielded 2-indol-1-yl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine **40**. The compound **40** acts as an AAA+ ATPase p97 inhibitor. The p97 AAA+ ATPase plays a key role in protein homeostasis, ERAD-mediated protein deprivation autophagy, chromatin remodeling, and reassembly of the Golgi. Inhibition of p97 induces apoptosis and cell death in tumor's. Lead optimisation efforts and SAR analysis employing various techniques for selective inhibition of p97-mediated ATP sensitivity through the D2 domain identified compound 68 as a potent inhibitor of enzyme activity. Nude mice bearing xenografts for human A549 lung carcinoma/HCP116 colon tumor showed potent inhibition of tumor growth. Based on its potency, the compound was promoted in Phase 1 clinical trials (Scheme-10).[12]



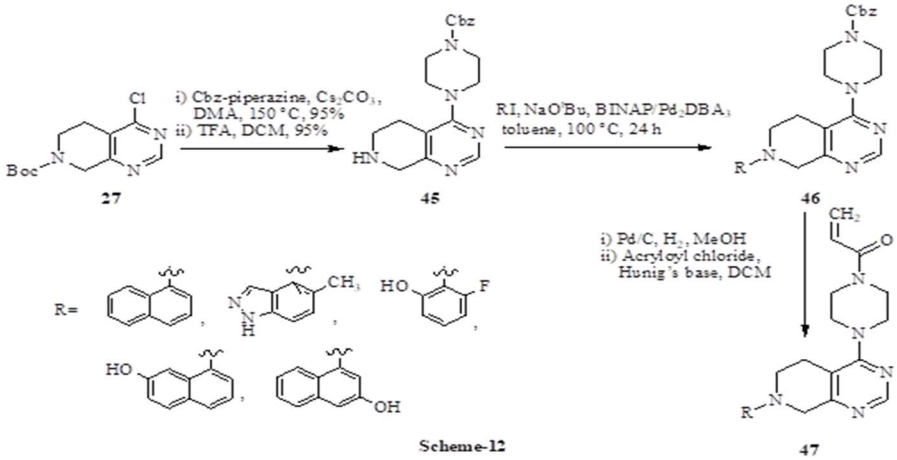
Scheme-10

The β-ketoester **7** and amidines **41** were reacted for the formation of the pyrimidine nucleus by using a basic medium, followed by chlorination to give the 4-chloro compounds **42**. Palladium-catalyzed coupling of boronic acids (Suzuki coupling) or Stille reagents with chloro compound **42** provided compound **43**. Further deprotection and aroylation afforded the desired products, benzoyl derivatives **44**. These molecules are instrumental in detecting neuropsychiatric disorders caused by the P2X7 receptor. P2X7 receptor is present in the CNS and plays a vital part in modulating neuroinflammation, and P2X7 antagonists were found to be effective in animal models with mood disorders. Few tetrahydropyrido[3,4-*d*]pyrimidines **44** were found effective as P2X7 antagonists in rat as well as ex vivo radio labelled binding assay. Further dog pharmacokinetic experiment showed little clearance (CL = 8 mL/min/kg) and an overall bioavailability is 35% (Scheme-11).[13]



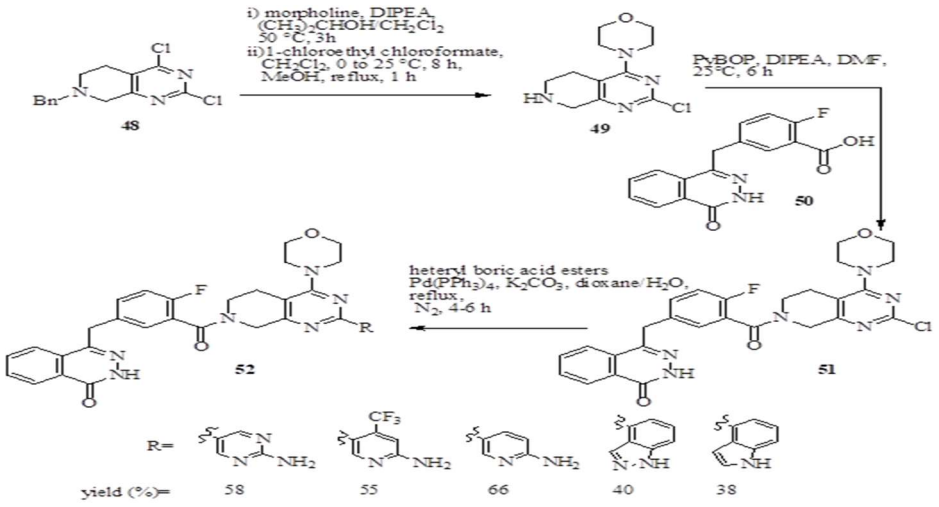
Scheme-11

Fell *et al.,* were synthesized tetrahydropyrido[3,4-*d*]pyrimidine **47** by amination of compound **27** with benzyl piperazine-1-carboxylate, deprotection with TFA to **45**, alkylation with RI to intermediate **46,** followed by reaction with acryloyl chloride. These tetrahydropyridopyrimidines **47** acted as KRAS-G12C irreversible covalent inhibitors with *in vivo* activity in protein modification assay, followed by tumor regression. (Scheme-12).[14]



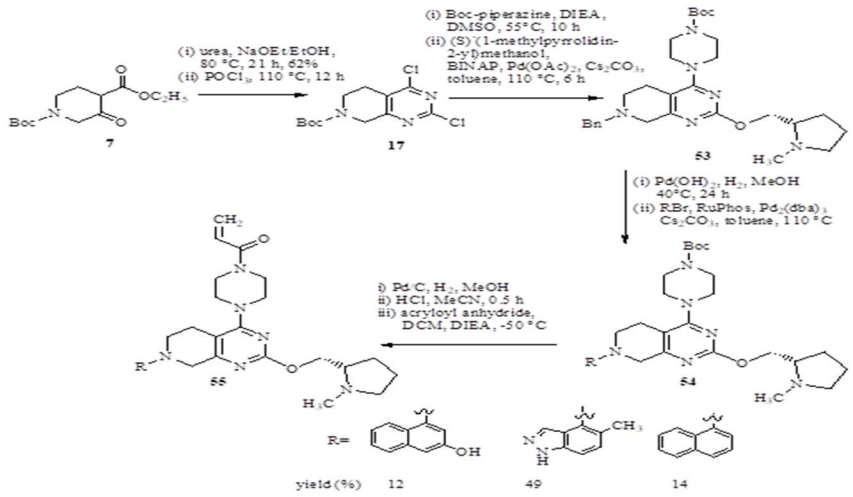
Scheme-12

Wang *et al*., substituted the chlorine atom at the 4th carbon of compound **48** with morpholine, followed by deprotection in the presence of an acidic medium to give intermediate **49.** Condensation of the resulting intermediate **49** with benzoic acid **50** using PyBOP and DIPEA produced intermediate **51.** Finally, **51** reacted with heteraryl boric acid esters in Suzuki coupling conditions, affording morpholino derivative **52**. These are novel dual PARP and PI3K inhibitors for cancer therapy, as the role of both these enzymes is instrumental in the repair of DNA single-stranded breaks (Scheme-13).[15]



Scheme-13

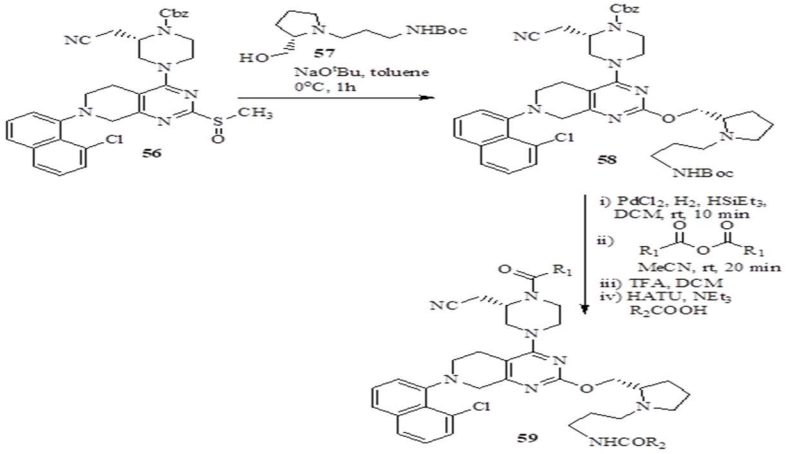
Using SBDD and screening for in vitro ADME facilitated the desired compounds as inhibitors of KRAS. The synthesis of desired tetrahydropyrido[3,4-*d*]pyrimidines **55** is commenced with the cyclisation of carboxylate **7** with NH_2CONH_2, followed by reaction with $POCl_3$ to afford compound **17**. The piperazine and alkoxy moieties are installed at C_4 and C_2 positions to produce **53**. The **53** was subjected to *N*-benzyl group deprotection, then arylation/heterylation leads to the formation of **54,** followed by deprotection and acryloylation to afford the final compounds **55**. A novel compound MRTX849 proved as a $KRAS^{G12C}$ inhibitor that binds irreversibly, enzyme bonding with cysteine 12. This compound possessed potent $KRAS^{G12C}$ inhibitory activity, enzyme selectivity, and enhanced oral bioavailability, facilitating durable complete responses in tumor-bearing mice (Scheme-14).[16]



Scheme-14

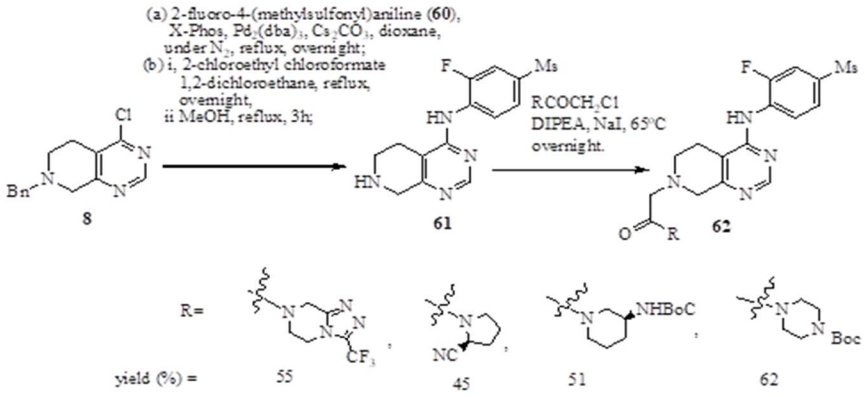
Morstein *et al.,* synthesized anti-cancer active tetrahydro-pyrido[3,4-*d*]pyrimidines **59** from **56** on reaction with **57** in the presence of NaO^tBu and deprotection of the resultant intermediate **58**, acylation of piperazine NH, Boc deprotection, followed by condensation with carboxylic acid. Crystal structure of $KRAS^{G12C}$ in

complex with MRTX849 identified solvent solvent-exposed site of the inhibitor, which facilitated the synthesis of lapidated analogues of MRTX849. Analogue C11-MRTX restricted the lateral mobility of KRAS, contributing to a reduction in diffusion rates, leading to the disruption of $KRAS^{G12C}$ non-clusters essential for signal transmission by the identified novel therapeutic agent (Scheme-15).[17]



Scheme-15

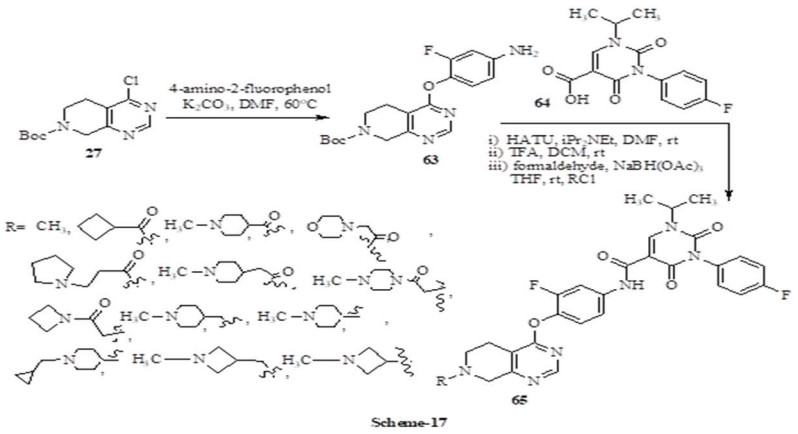
The compound **8** was reacted with 1° amine **60** in the presence of Pd catalyst, resulting in intermediate diamine **61**, which was converted to compound **62** by alkylation. This approach of merged pharmacophores of GPR119 agonists and DPP-4 inhibitors resulted in a series of tetrahydro pyrimidine compounds having dual modulators of GPR119 and DPP-4 involved in insulin release and secretion of GLP-1 peptide related to the metabolism of glucose homeostasis (Scheme-16).[18]



Scheme-16

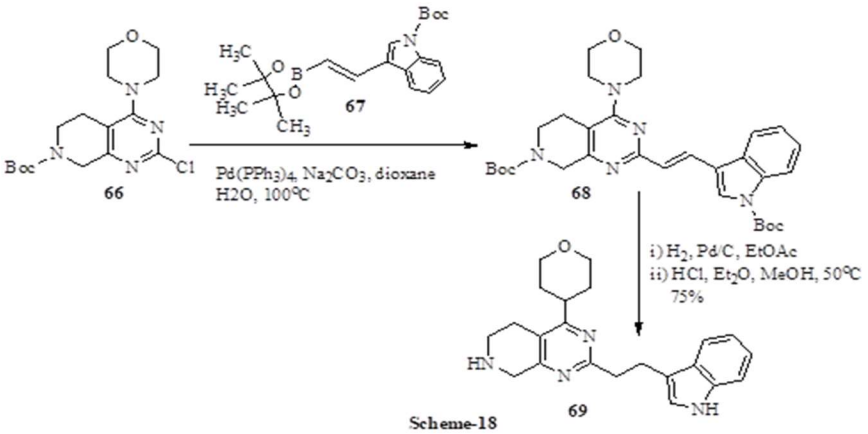
Axl Inhibitors, 5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidines **65**, are synthesized from compound **27**. The compound **27** was reacted with 4-amino-2-fluorophenol in the presence of ^{t}BuOH to isolate arylamine **63**. The intermediate **63** was condensed with carboxylic acid **64** to afford the target compounds. Ax1/Mer dual inhibitors were found to exhibit retinal toxicity in mice. Representative compounds showed potent inhibitory activity against Ax1 and did not exhibit any retinal toxicity with a promising pharmacokinetic profile in mice (Scheme-17).[19]

A novel screening strategy of drug discovery, X-ray crystallography of bound compound with recombinant CYP121A1 of *Mycobacterium tuberculosis* in combination with phenotypic analysis, was reported by Frederickson *et al.,* Upon screening a battery of compounds, several of them showed promising activity against Mtb strain H37Rv. One molecule of them showed potent activity and an X-ray hit against CYP121A1 in X-ray crystallography screening. Analogues of this compound was synthesized and screened for their activity.



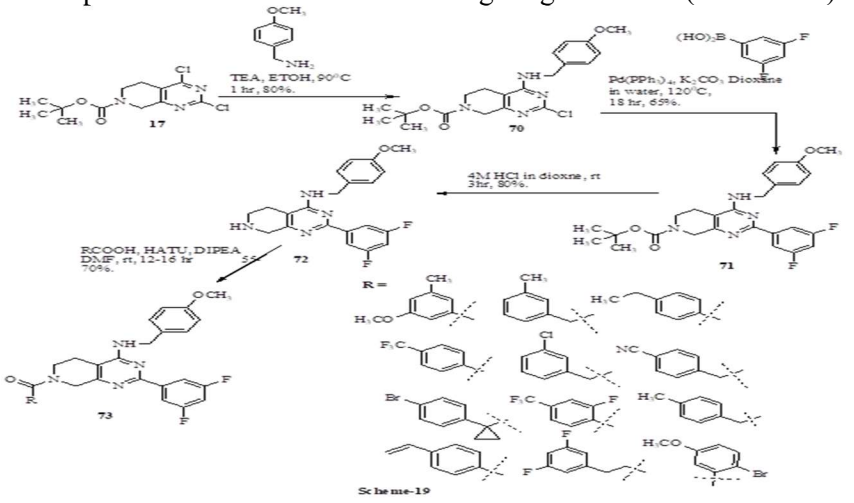
Scheme-17

Synthesis of compound **69** was carried out from **66** by Suzuki coupling with **67** to yield **68,** followed by reduction and deprotection. This compound showed potent activity in the pan assay activity against CYP121A1 by inhibiting the formation of mycocyclosin from cyclic dipeptide cYY. This compound was further proved to be an active inhibitor *in vivo,* resulting in the development of a drug lead candidate (Scheme-18).[20]



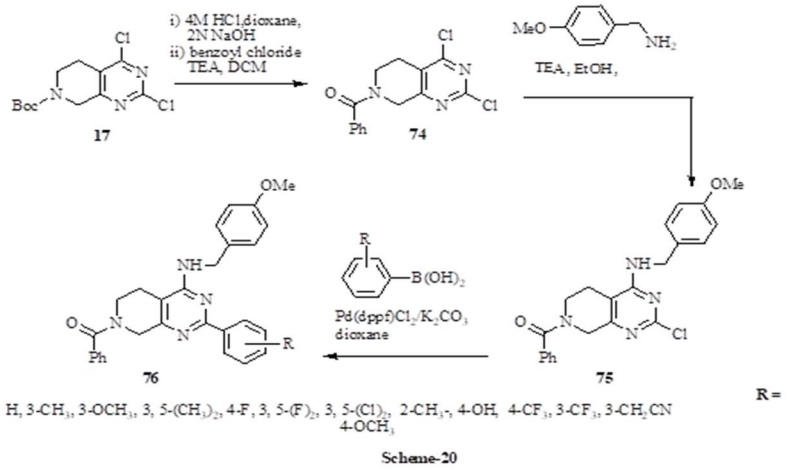
Scheme-18

Vasantha *et al.,* have synthesized anti-leukemic agents, tetrahydro-pyrido[3,4-*d*]pyrimidines **73**, from compound **17** by amination to **70**, Suzuki coupling with 3,5-difluorophenylboronic acid to amine **71**, deprotection to compound **72,** followed by condensation with various aryl carboxylic acids. *In vitro* evaluation of these compounds against two cell lines (HEK293 & K562-WT) and two drug-resistant cell lines (K562-IR1 & K562-IR2) revealed anticancer activity. One of the compounds, **72,** exhibited significant selectivity and can be a potential candidate for overcoming drug resistance (Scheme-19).[21]



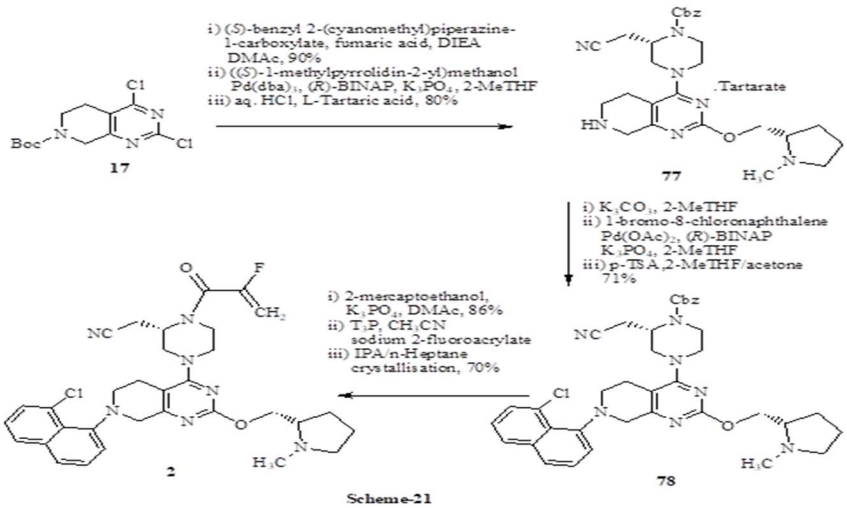
Scheme-19

The compound **17** was deprotected with HCl, then reacted with benzoyl chloride to compound **74**, aminated to compound **75,** followed by reaction with aryl boronic acid under Suzuki coupling conditions to isolate tetrahydropyrido[3,4-*d*]pyrimidines **76**. 4-Hydroxy derivative of **76** displayed antifungal activity as potent as Itraconazole. Further, 4-trifluoromethyl and 3-trifluoromethyl derivatives of **76** exhibited encouraging antibacterial activity than Amoxicillin (Scheme-20).[22]



Scheme-20

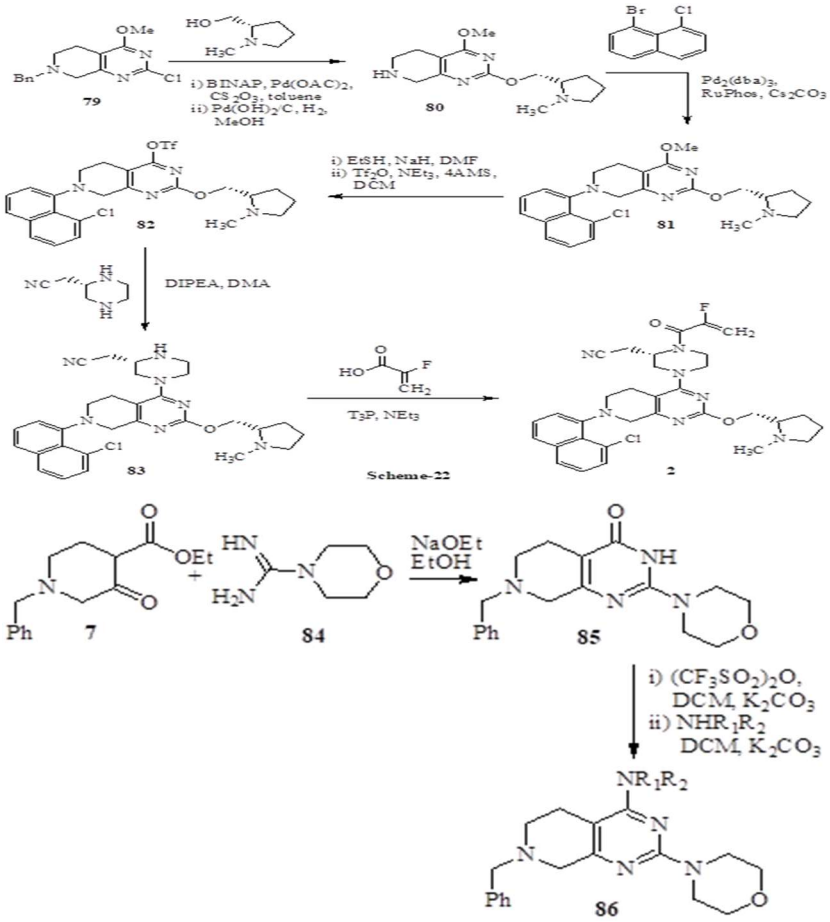
Chen *et al.,* have developed the manufacturing process for Adagrasib (**2**), starting with compound **17**. The Cbz-masked piperazine was introduced at the 4-position of **17**, then prolinol was installed at C-2.



Scheme-21

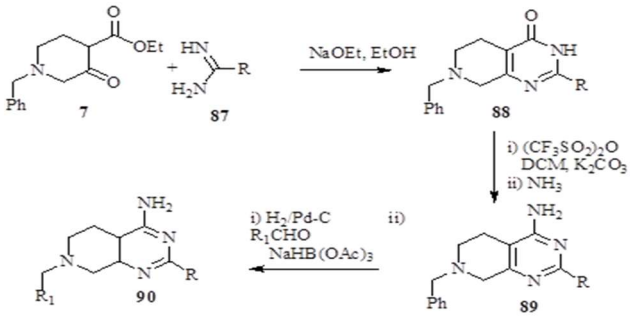
Position to C−O bond using palladium-catalyst, followed by Boc-deprotection to isolate **77**. Buchwald Hartwig amination of chloronaphthyl bromide by the resulting **77** was achieved to generate **78**. Unmasking the Cbz-protected piperazine employing 2-mercaptoethanol and coupling of sodium 2-fluoroacrylate in the presence of n-propanephosphonic acid anhydride (T_3P)-mediated to complete the synthesis of Adagrasib (**2**, Scheme-21).[23] Alternatively, Snead et. al also developed the commercial manufacturing route to Adagrasib (**2**) from compound **79**. Installation of alkoxy group at C-2 by Suzuki coupling in presence of BINAP/Pd catalyst to produce **80**, reaction of **80** with 1-bromo-8-chloronaphthalene to compound **81**, treatment with NaH in presence of thioethanol then activated with trifluoromethanesulfonic anhydride to produce compound **82**, nucleophilic reaction with 2-((*S*)-piperazin-2-yl)acetonitrile to compound **83** followed by reaction with 2-fluoroacrylic acid afforded compound **2 (**Scheme-22**)**.[24]

The tetrahydropyrido[3,4-*d*]pyrimidines **86** were synthesized by reaction of compound **7** and morpholine-4-carboxamidine (**84**) in basic medium, followed by treating the resulting **85** with triflic anhydride and secondary amines (Scheme-23).[25]



Scheme-23

Kuznetsov and Chapyshev reacted compound **7** with formamidine derivative **87** to get **88.** Subsequent treatment of **88** with triflic anhydride and aqueous ammonia gave corresponding amine **89,** and deprotection followed by reductive amination of aldehydes yielded tetrahydropyrido[3,4-*d*]pyrimidines **90 (**Scheme-24).[26,27]



R = 1-pyrrolidinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl
R_1 = 4-EtC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, 2-FC$_6$H$_4$, 2-HOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 2-EtOC$_6$H$_4$, 2,4-(MeO)$_2$C$_6$H$_3$, 2-OH-4-MeOC$_6$H$_3$, 3,4-(MeO)$_2$C$_6$H$_3$, 3-MeO-4-HOC$_6$H$_3$, 3-OH-4-MeOC$_6$H$_3$, 3-MeO-4-EtOC$_6$H$_3$, 3-HOCH$_2$-4-MeOC$_6$H$_3$, 3-EtO-4-HOC$_6$H$_3$, 3,5-(MeO)$_2$C$_6$H$_3$, 2,4,5-(MeO)$_3$C$_6$H$_2$, 2-thienyl

Scheme-24

CONCLUSION

In conclusion, we provide an impressive summary of the preparation and therapeutic activity of compound **1** derivatives, covering the literature up to September 2024, and arranged keeping in view of chronological order and biological activity. From the literature, it is implied that compound **1** has appeared as a privileged

platform for the synthesis of various compound **1** derivatives by the modifications at 2nd, 4th, and 7th positions with Suzuki coupling, nucleophilic substitution, and electrophilic substitution, respectively. In addition to Adagrasib, a marketed drug from this class of heterocycles, many derivatives have exhibited potent biological activity. Facile synthesis and its broad spectrum of pharmacological activities encouraged the scientists to develop more drug candidates from scaffold **1**.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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