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2-AMINOPYRIDINE – A CLASSIC AND TRENDY PHARMACOPHORE

MARIA MARINESCU*

Department of Organic Chemistry, Biochemistry and Catalysis, Faculty of Chemistry, University of Bucharest, Sos. Pandurilor 90-92, 050663

ABSTRACT

Chemists and pharmacists have exploited the classical and small molecules, due to their ability to be easily grafted with different groups, being able to bind to other more complicated structures to achieve the synthesis of new structures with various biological properties. Among the various 6-membered heterocyclic compounds, 2-aminopyridines have drawn special attention because of the various pharmacologically activities associated with the presence of it in targeted molecules. Researchers have shown that the presence of a small molecule of 2-aminopyridine is an advantage for the medicinal properties of the target molecule, whether it is simple molecule, with just a few groups on it, or is a complicated one, with more heterocycles present in the structure. A number of drugs containing a residue of 2-aminopyridine are already offered on the market, such as piroxicam, tenoxicam, sulfasalazine with anti-inflammatory properties, delavirdine, as anti-HIV drug, sulfapyridine, as antibacterial and tripelenamine as antihistaminic drug. Thus, simple or complex structures with grafted moiety 2-aminopyridine, have been shown to be effective as antitumoral, anti-Alzheimer, antidiabetic, antimicrobial, antiviral, analgesic, anti-inflammatory, antiparasitic, antimalarial, antihistaminic, anticonvulsant, Renin-inhibitors, n-NOS-inhibitors, CXCR1/2 inhibitors, JNK1 inhibitors, PKC inhibitors, Syk-inhibitors and also with cardiac activity. This review presents the most representative literature which highlights the role of 2-aminopyridine as pharmacophore in various compounds with medicinal properties. The study highlights the central role of 2-aminopyridine moiety in the pharmacological properties of the synthesized molecule.

KEYWORDS: *2-Aminopyridine, Pharmacophore, Biological activity, Antitumoral, Anti-Alzheimer, Analgesic, Antimicrobial.*

MARIA MARINESCU*

Department of Organic Chemistry, Biochemistry and Catalysis, Faculty of Chemistry, University of Bucharest, Sos. Pandurilor 90-92, 050663

***Corresponding Author**

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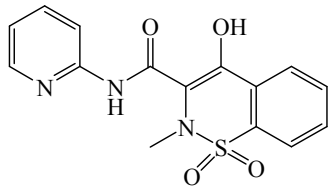
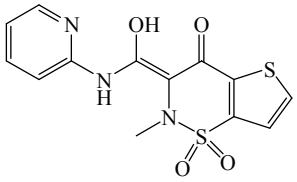
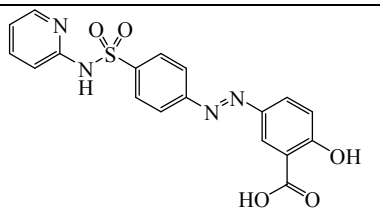
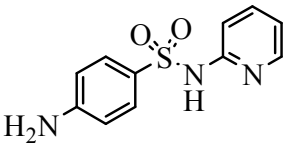
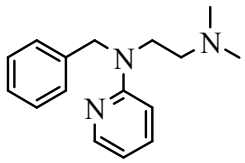
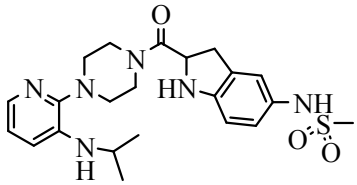
INTRODUCTION

Among the nitrogenous heterocycles, aminopyridines and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists due to their exceptionally broad spectrum of biological activities as well as their use as important binding units in the molecular design of synthetic receptors. 2-Aminopyridine, one of three isomeric aminopyridines, is produced by the reaction of sodium amide with pyridine, the Chichibabin reaction as a colourless solid that is used in the production of the drugs piroxicam, tenoxicam, sulfasalazine, sulfapyridine, tripelennamine and delavirdine[1] (Table-1).

Table 1
Marketed drugs having 2-aminopyridine pharmacophore

 **Piroxicam (Anti inflammatory)**	 **Tenoxicam (Anti inflammatory)**	 **Sulfasalazine (Anti inflammatory)**
 **Sulfapyridine (Antibacterial)**	 **Tripelennamine (Anti histaminic)**	 **Delavirdine (Anti-HIV)**

2-Aminopyridines are key structural cores of bioactive natural products, medicinally important compounds, and organic materials and thus, extremely valuable synthetic targets.[2] Many naturally compounds having pyridine moiety show interesting biological and pharmacological activities.[3] Pyridine derivatives have been used for regulation of arterial pressure[4] and cholesterol levels in blood.[5] Some of them constitute an important class of antitumor compounds.[6] 2-Amino-pyridines have been identified to possess a wide range of biological activities such as antibacterial, antifungal, antihistaminic, cardiotonic, antiviral, anticonvulsant, anti-diabetic, analgesic, anti-Alzheimer, antiparasitic, anti-inflammatory and inhibitors of neuronal nitric oxide (Figure 1).[3,7-10]

2. 2-AMINOPYRIDINE AS ANTITUMORAL AGENT

Cancer is one of the main diseases causing the death of millions of people annually across the globe. This determined the researchers to intensify their studies for finding new antitumoral agents. Nowadays, cancer treatment includes small heteroaromatic rings as basis molecules for chemotherapy. It is imperative for the new anticancer drugs to obey major requirements: selectivity and better activity.[8]

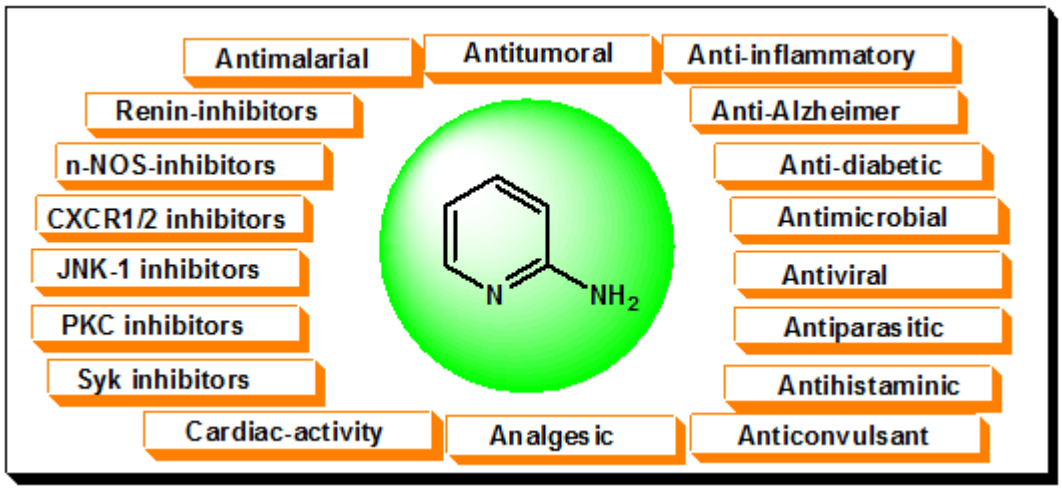


Figure 1
Pharmacological properties of 2-aminopyridine compounds

Cai et *al.,* (2008) synthesized a series of pyrrolopyridine- and aminopyridine compounds as potent inhibitors of Met kinase activity. c-Met kinase is a promising therapeutic target for cancer being responsible for the emergence of the resistance mechanism in chemotherapy, radiotherapy and other RTK based target therapy. 2-Aminopyridine **1** (Figure 2) exhibited good pharmacokinetic properties in mice and significant antitumor activity in a human gastric carcinoma xenograft model. Also, compound **1** displayed potent inhibition of Met kinase activity with an IC_{50} value of 350 nM, being three-fold more potent than the corresponding pyrrolopyridine analog.[9]

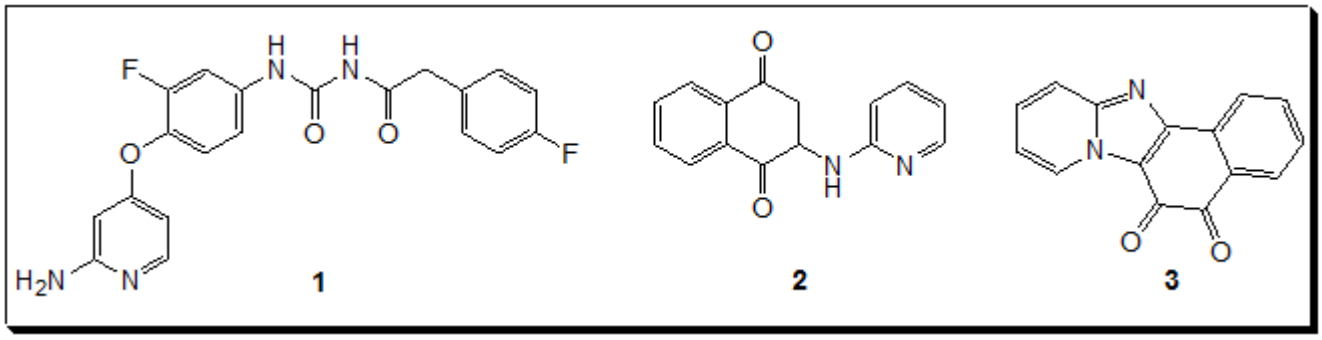


Figure 2
2-Aminopyridines 1-3 - antitumoral agents

Tapia group, (2009) reported the synthesis of pyridylaminonaphthoquinones by microwave-assisted reaction of 2,3-dichloro-1,4-naphthoquinone with aminopyridines. *In vitro* cytotoxicity of the synthesized naphthoquinone **2** and **3** (Figure 2) against MCF-7 breast cancer cell line was evaluated with a IC_{50} value of 85.70 and 6.87 µM respectively. On the basis of these IC_{50} values, compound **3** was the most active although less potent than daunorubicin. The results are consistent with the concept that a planar conformation for a tricyclic structural pattern is a requirement for antitumor activity.[10] There is current interest in the therapeutic potential of inhibitors of CHK2 especially in cancer where DNA-damaging agents remain a central component of treatment. Checkpoint kinase 2 (CHK2) is a serine/threonine kinase which plays an important part in the complex signalling networks responsible for the maintenance of mammalian genomic integrity and repair of damaged DNA. It is also possible that only inhibition of CHK2 could exert an antitumor effect because in some cancer cell lines, CHK2 is highly activated. Hilton et *al.*, (2010) synthesized and identified 5-(hetero)aryl-3-(4-carboxamidophenyl)-2-aminopyridine as inhibitors of CHK2. The inhibition of a panel of 24 kinases was determined for compounds **4** and **5** (Figure 3) using a microfluidic substrate phosphorylation assay. Both compounds showed generally good selectivity for CHK2 compared to other kinases (IC_{50} 0.7 µM and 0.028 µM respectively) in the set, and this was reflected in the higher Gini coefficients, 0.75 and 0.77 respectively. The Gini coefficient assesses the cumulative inhibition measured for the compounds across all the kinases in the panel, with values close to 1 indicating specific inhibition of a single kinase. Compound **5** showed good cellular inhibition of CHK2 activity with half maximal effects at approximately 5 µM.[11]

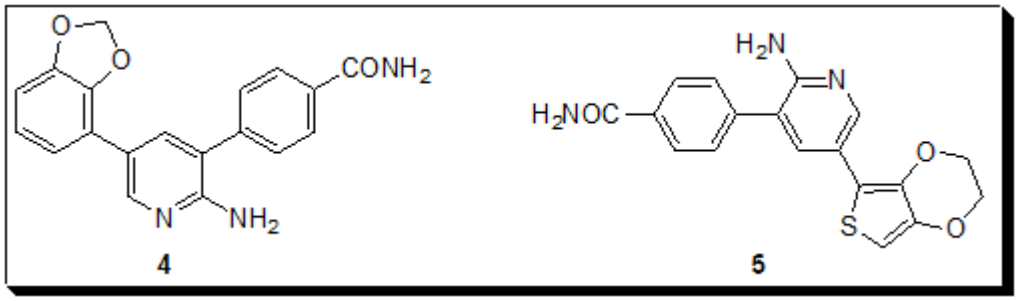


Figure 3
2-Aminopyridines 4-5 - antitumoral agents

c-Met has recently attracted considerable interest as a therapeutic target based on the discovery that aberrant c-Met activity leads to the formation of various cancers including lung, gastric, renal, ovarian, prostate, and liver cancers. c-Met is a receptor tyrosine kinase (RTK) and plays important roles in cell survival, proliferation, migration, and angiogenesis under physiological conditions. A series of benzoxazole-substituted aminopyridine-based inhibitors 6-14 (Figure 4) of c-Met kinase was synthesized by Cho et *al.*, (2010) starting from carbonyl chlorides indicated as moieties and the precursor piperidine. 2-Aminopyridine **6** showed good c-Met inhibitory potency (IC_{50} 3 nM), low affinity to hERG and favorable pharmacokinetic properties in rats. The docking calculations for this compound showed that **6** bound c-Met very tightly (9.56 kcal/mol). The strong interaction of **5** with c-Met is attributed to H-bonds of both the 2-aminopyridine moiety with terminal residues present in molecule, and to the interactions of acetyl group.[12]

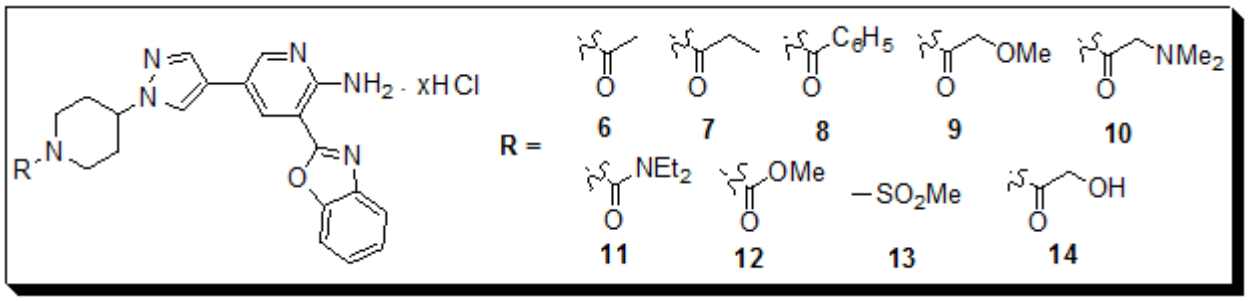


Figure 4
2-Aminopyridines 6-14 - antitumoral agents

Lin et *al*., (2010) reported the synthesis of tetrasubstituted pyridines 15-17, *via* pyridine N-oxide 18 (Figure 5), using a Mitsunobu coupling. In general, introduction of an amino group maintained or slightly increased the enzymatic potency against all three AKT isoforms, as well as cellular potency in both anti-proliferation and mechanistic assays (15-17). In case of 17 the amino group also helped to reduce CYP450 3A4 inhibition and hERG channel inhibitory potency (IC_{50} = 10.4 μM). Compound 17 also demonstrated a robust *in vivo* pharmacodynamic effect and dose-dependent inhibition of tumor growth in a BT474 xenograft.[13] Yousef et *al.,* (2011) prepared some anticancer 4-(2-pyridyl)-3-thiosemicarbazides derivatives 19-21 (Figure 5). All synthesized compounds were studied using *in vitro* growth of a transplantable murine tumor cell line (Ehrlich Ascites Carcinoma) and *in vivo* induced hepatocellular carcinoma. Thiosemicarbazide 19 has remarkably decreased the viable ascitic cell count as indicated by trypan blue dye exclusion assay. The result was confirmed by *in vivo* results, because 19 prolonged the lifespan of (EAC) bearing-mice. The tumor inhibition determined of all compounds was demonstrated by significant improvement in blood picture (hemoglobin, RBC and WBC). Compound 19 showed a strong cytotoxic activity (IC_{50} 18.7 mg/mL).[14] Zhang and Li, (2012) synthesized and evaluated a series of benzamide-based histone deacetylases (HDACs) inhibitors possessing N-(aminopyridine) moiety. Intermediate cinnamic acids were obtained *via* Knoevenagel reaction. Their HDACs inhibitory effect are evaluated on cell proliferation against human cancer cells: prostate carcinoma (PC-3), breast carcinoma (MDA-MB-435S) and leukemia (Hut78, K562 and Jurkat E6-1).The most potent compounds have been found the derivatives with N-(2-amino-4-pyridine) benzamide moiety. All compounds were evaluated *in vivo* carried out female Sprague Dawley rats. The antiproliferative activity was significantly improved by introduction of appropriate substituent on the terminal aryl group acting as the surface-recognition.

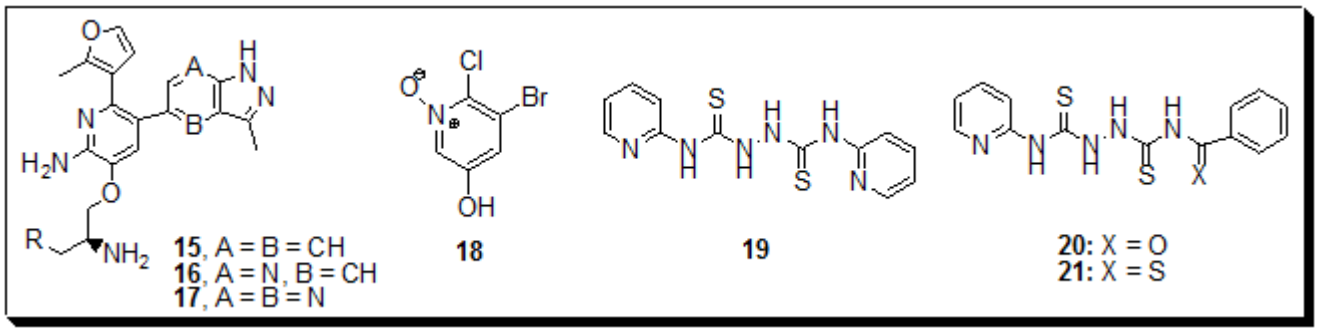


Figure 5
2-Aminopyridines 15-21 - antitumoral agents

Compound 22 (Figure 6) had the significant potency on cell proliferation against PC-3 cells with IC_{50} value of 1.1 μM. At a dose of 50 mg/kg administered, the 22 inhibitor was well tolerated and a 37% tumor growth inhibition (TGI) was observed without significant weight loss.[15]

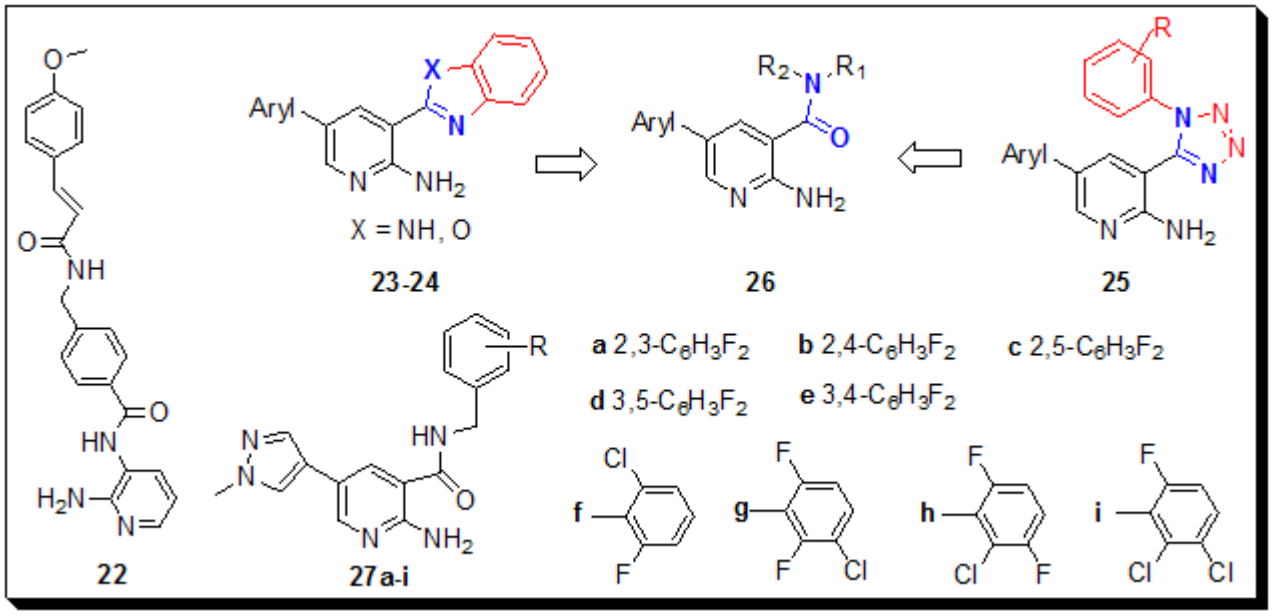


Figure 6
2-Aminopyridines 22-27 - antitumoral agents

Zhang et *al.,* (2012) discovered one novel c-Met kinase inhibitors by the replacement of aryl (imidazole, oxazole and tetrazole) from 23-25 (Figure 6) with the amide bond in the analogs 26. Novel inhibitors 27 were synthesized starting from 2-aminonicotinic acid *via* Suzuki coupling. It was found that compounds 27 a-i exhibited moderate activity against c-Met with IC_{50} ranging from 7.00 to 0.41 μM. Derivatives bearing 2, 5-difluoro (27c) and 3,4-difluoro (27e) benzyl groups displayed more potent c-Met inhibition than other difluoro substituted analogs (27a, 27b, 27d). The activity did not significantly change with the introduction of *o,o'*-disubstituents (27f–27i).[16] Lee et *al.*, (2012) synthesized a series of hydroxybenzoxazoles of 2-aminopyridine 28-29 (Figure 7), evaluated their c-Met kinase inhibitory activity (Table-2) and studied structure-activity realationship. Compound 28j displayed potent c-Met (IC_{50} = 0.2 nM) and Flt3 IC_{50} = 0.034 μM inhibitory activity, with moderate activity in the Hs746T proliferation assay (IC_{50} = 0.035 μM). 28d exhibited potent inhibitory activities against Flt3 (IC_{50} = 4 nM), mutant Flt3 (D835Y, IC_{50} = 0.3 nM), Ron (IC_{50} = 0.014 μM), and Aurora A (IC_{50} = 0.09 μM). Also, compound 29 exhibit good potent c-Met inhibitory activity (IC_{50} = 0.014 μM). Compound 28j have potent c-Met (IC_{50} = 0.2 nM) and Flt3 IC_{50} = 0.034 μM inhibitory activity, with moderate activity in the Hs746T proliferation assay (IC_{50} = 0.035 μM). 28d exhibited potent inhibitory activities against Flt3 (IC_{50} = 4 nM), mutant Flt3 (D835Y, IC_{50} = 0.3 nM), Ron (IC_{50} = 0.014 μM), and Aurora A (IC_{50} = 0.09 μM). Compound 29 exhibit good potent c-Met inhibitory activity (IC_{50} = 0.014 μM).[17] Palmer et *al.*, (2012) synthesized 3-methoxy-2-aminopyridines as potent inhibitors of the oncogenic kinaze bRAF for the treatment of melanoma and colon cancer.

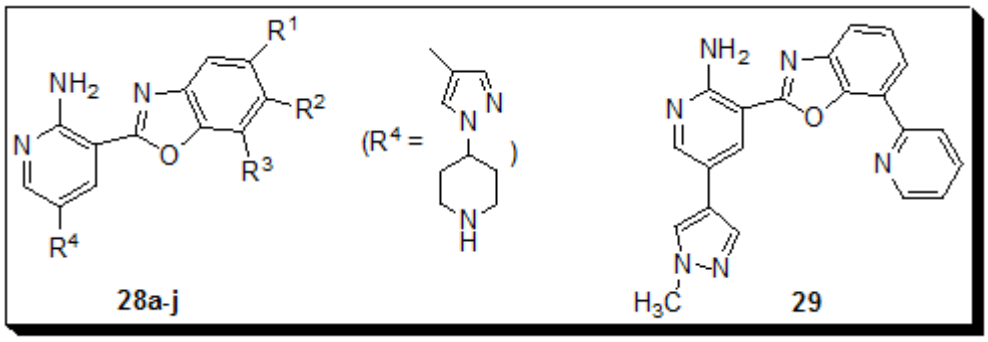


Figure 7
2-Aminopyridines 28-29 - antitumoral agents

Table 2
***Potent c-Met inhibitory activities of compounds 28a-j*[17]**

Compound	R^1	R^2	R^3	c-Met IC_{50} (μm)
28a	H	H	H	0.080
28b	Cl	H	H	0.053
28c	Cl	H	F	0.041
28d	H	OH	H	0.019

28e	H	OH	Et	0.009
28f	H	3-Pyridinyl	H	0.028
28g	H	H	2-Pyridinyl	0.0016
28i	H	H	4-MeO-Ph	0.077
28j	H	OH	CH_3	0.0002

(S)-1-((4-(3-(6-amino-5-methoxy pyridin-3-yl)-1-isopropyl-1*H*-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-ol 30 (Figure 8) was identified as a potent RAF inhibitor with excellent kinase selectivity *in vivo* (pMEK IC_{50} = 6.5nM (b-RAF^{V600E} cellular assay)).[18]

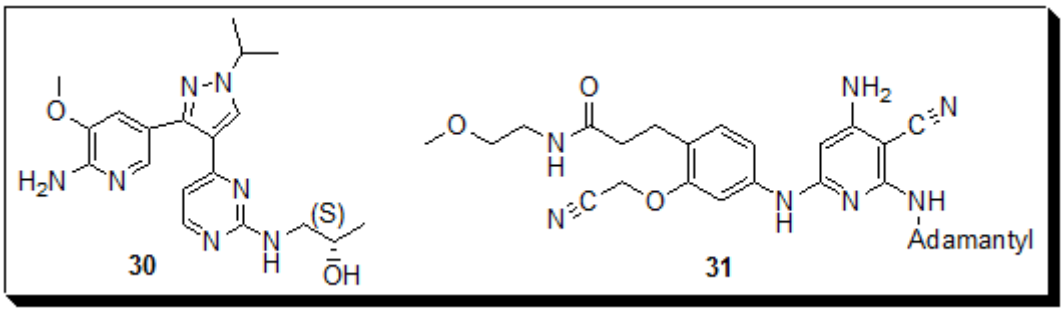


Figure 8
2-Aminopyridines 30-31 - antitumoral agents

High levels of mRNA and protein are strong correlated with the presence of human cancer cells, and especially with tumor in breast cells. Kusakabe et *al.*, (2015) synthesized 2-aminopyridine 31 (Figure 8) *via* Suzuki coupling that exhibited no significant inhibition for 287 kinases as well as improved cellular Mps1 and antiproliferative activities in A549 lung carcinoma cells (cellular Mps1 IC_{50} = 5.3 nM, A549 IC_{50} = 26 nM).[19] Liu et *al.*, (2015) synthesized *via* a Suzuki–Mukiyama coupling a series of aminopyridines as potent FMS-like tyrosine kinase 3 (FLT3) inhibitor in Phase III clinical development of acute myeloid leukemia. Compound 32 (Figure 9, pFLT3 IC_{50} = 0.271 nm) have a very good response in delaying the progression of tumor at the 1 mg/kg dose. Derivative 32 inhibited the progression of tumor in a dose-dependent manner, even at an extremely low dose of 0.1 mg/kg. At the higher doses, tumors regressed completely and long-lasting tumor growth suppression persisted for an extended period after dosing was halted.[20] Zhao et *al.*, (2015) identified new JAK2 inhibitors for the treatment of several types of cancers (colon, prostatic, pancreatic) by using Surflex-Dock software and testing 3010 compounds with known chemical structures. Compounds 33 (IC_{50} = 6.9 μM) and 34 (IC_{50} = 12.2 μM) showed better JAK2 inhibition, therefore this validate the design approach.[21]

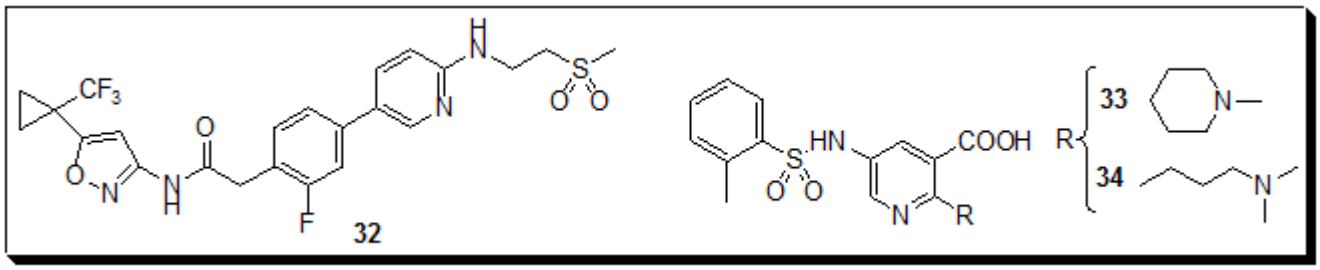


Figure 9
2-Aminopyridines 32-34 - antitumoral agents

3.2-AMINOPYRIDINE AS ANTI-ALZHEIMER

Alzheimer's disease (AD) is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. This causes about 60-70% of all cases of dementia.[22] The age-related neurodegenerative process is characterized by a progressive loss of cognitive abilities: memory, language skills, disorientation, attention and depression. Amyloid-β ($Aβ$)[2] deposits, τ-protein aggregation, oxidative stress or low levels of acetylcholine are thought to play significant roles in the pathology of the disease.[23] Samadi et *al.*, (2010) synthesized 2-aminopyridine-3,5-dicarbonitriles and evaluated their activities as inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Compounds 35-38 (Figure 10) showed neuroprotection with values in the range 37.8–31.6% in SH-SY5Y neuroblastoma cells stressed with a mixture of oligomycin-A/rotenone. IC_{50} (AChE inhibition) values of 22.7 and 3.5 μM respectively were found for 35 and 36 and 3.8 μM (BuChE inhibition) for 2-aminopyridine 39.[24] The proteolytic enzyme β-secretase (BACE1) plays a central role in the synthesis of the pathogenic β-amyloid in Alzheimer's disease. Malamas et *al.*, (2010) reported synthesis of novel pyrrolyl-2-aminopyridines 40-42 as BACE1 inhibitors. The pyrimidinyl analog 40 was the most potent compound with an IC_{50} value of 100 nM for BACE1.

Aminopyridine 40 (Figure 10) also demonstrated high brain permeability with a brain to plasma ratio of 1.1, despite an increase of the compound's total polar surface area (TPSA = 79). Also 41 and 42 analogs have good IC_{50} values of 0.29 and 0.41 μM respectively. Starting from structure of BACE1 inhibitor 43 (Figure 11) established by Murray group,[25]

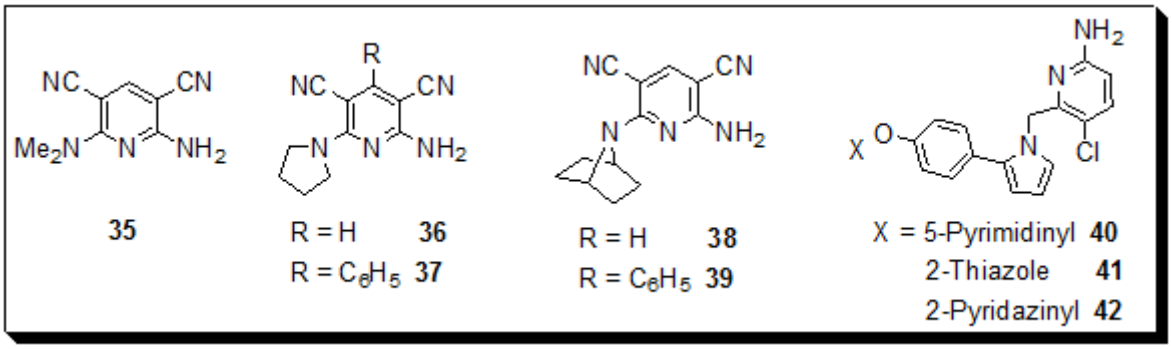


Figure 10
2-Aminopyridines 35-42 – anti-Alzheimer agents

Konno et *al*., (2015) synthesized new 2-aminopyridines 44-47 as potential BACE1 inhibitors using Sonogashira method. Compound 44 exhibited a greater inhibitory activity of 2.0 μM with a inhibition of 56%. In the same conditions, 45-47 have a inhibitory activity of about 20%.[26] Lee et *al*., (2016) evaluated 2-pyridylbenzithiophenes and 2-pyridylbenzothiazoles 48-51 as potential PET (positron emission tomography) tracers for imaging Aβ plaques in a living brain. (S)-configured PET tracers, (S)-[^{18}F]-48 and (S)-[^{18}F]-49, exhibited a 2.8 and 4.0-fold faster brain washout rate at a peak/30 min in the mouse brain than the corresponding (R)-configured PET tracers despite there being no meaningful difference in binding affinities toward Aβ plaque. All compounds exhibited high binding affinities, and a specific binding profile to Aβ plaque, which was confirmed by *in vitro* autoradiography with sections of postmortem AD and healthy brains, showing the specific staining showing the specific staining of the outer AD brain region. The R/S racemate 50-51 exhibited improved brain washout properties compared to 3-[^{18}F] fluoropropyl substituted molecules.[27]

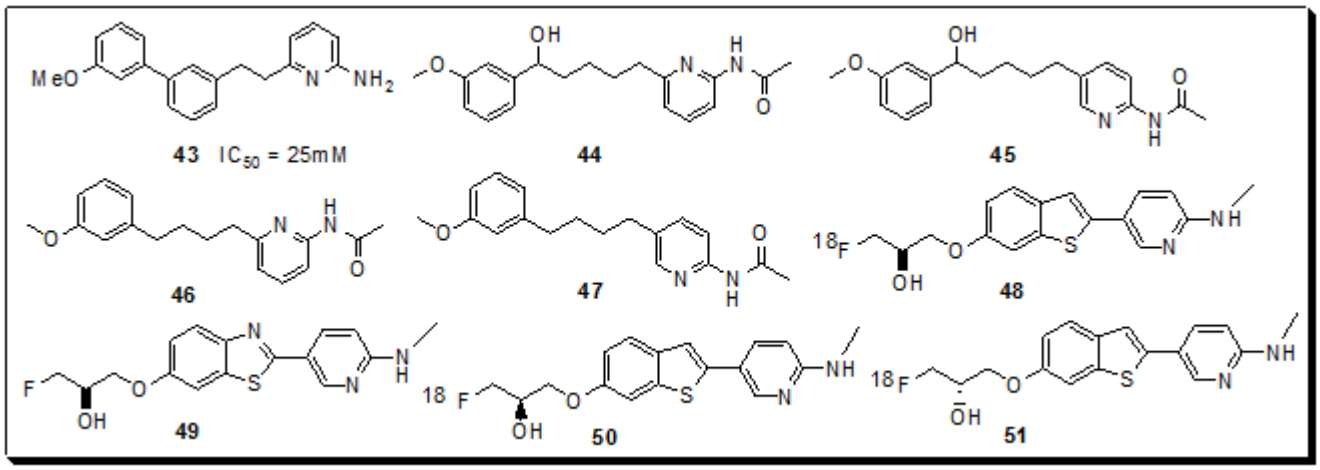


Figure 11
2-Aminopyridines 43-51 – anti-Alzheimer agents

4.2-AMINOPYRIDINE AS INHIBITOR OF NEURONAL NITRIC OXIDE SYNTHASE

Inhibition of neuronal nitric oxide synthase (nNOS) has therapeutic benefits in various neuro-degenerative diseases like Parkinson's disease and neuronal damage resulting from stroke. Also, this inhibition must be achieved without effect on the other isoforms of NOS, endothelial (eNOS) and inducible (iNOS). Inhibition of eNOS could lead to side effects such as hypertension, and inhibition of iNOS could result in a higher probability of Alzheimer's disease. Lawton et *al.,* (2009) designed a series of 2-aminopyridines potent and isoform selective inhibitors of nNOS *via* Mitsunobu reaction and tested their ability to inhibit the three NOS isoforms using an established *in vitro* assay. The secondary amine of the pyrrolidine ring of 52 (Figure 12) interacts with a key aspartate residue in nNOS. The secondary amine adjacent to the pyrrolidine was replaced with an ether linkage to form 53 and an amide linkage to form 54. Replacing the secondary amine in the chain with an ether linkage gave 55. The compounds 53-55 were tested for activity against the NOS isoforms (Table-3), and it was discovered that having an ether next to the pyrrolidine was a beneficial modification, but that having an ether in the chain resulted in a significant decrease in potency.[28] Ji et *al*., (2010) synthesized a series of *trans*-

substituted pyrrolidinomethyl 2-aminopyridines. A structure-activity relationship led to the discovery of low nanomolar nNOS inhibitors for (±)-56 and (±)-57 (Table-3) with more than 1000-fold selectivity for nNOS over eNOS. Only enantiomerically pure isomer 58 (3′*R*, 4′*R*) can induce enzyme elasticity to result a new type of nNOS

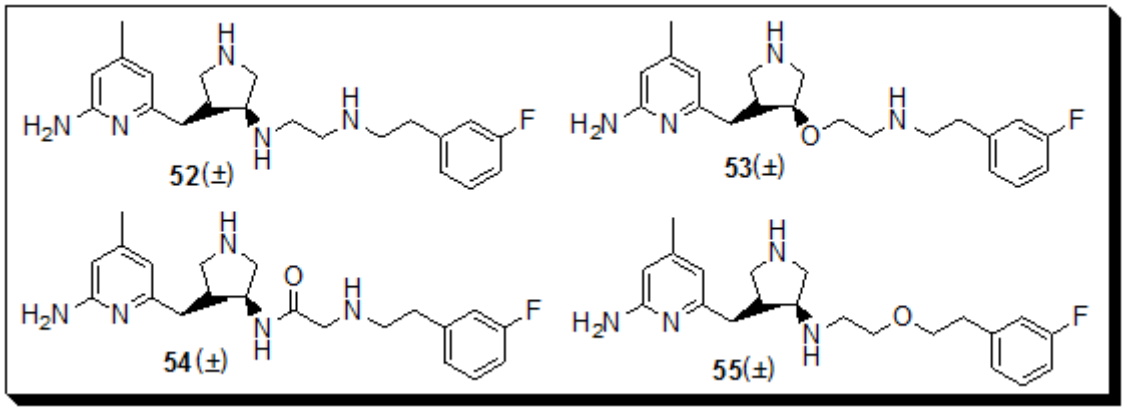


Figure 12
2-Aminopyridines 52-55 – inhibitor of neuronal nitric oxide synthase

Table 3
Inhibition of three izozymes of NOS by 52-55

K_i/ Compound	52	53	54	55	56	57	58
K_i (nNOS) (μM)	0.014	0.015	0.053	0.4	0.088	0.048	193.5
K_i (eNOS) (μM)	28	31	27	33	123.9	49.07	18.780
K_i (iNOS) (μM)	4	9.5	5.4	4	18.17	26.59	18.060

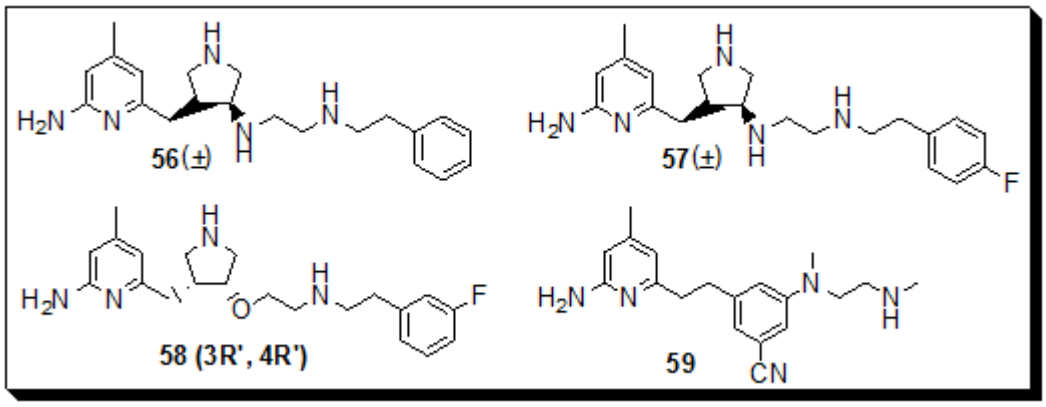


Figure 13
2-Aminopyridines 56-59 – inhibitor of neuronal nitric oxide synthase

inhibition.[29] Khang et *al.,* (2015) synthesized 2-aminopyridines with special geometry, to avoid the hydrophobic pocket that differentiates human and rat nNOS. Compound 59 (Figure 13) exhibits very promising K_i values, of 24 and 55 nM for rat and human nNOS, respectively. Also 59 has 18% oral bioavailability.[30]

5.2-AMINOPYRIDINE AS ANTIDIABETIC

Diabetes mellitus is a chronic metabolic process characterized by high levels of glucose in the blood resulting from insulin deficiency, insulin action or both.[31] Patients with diabetes mellitus are at high risk for developing long-term complications including neuropathy, nephropathy, retinopathy and cardiovascular disease.[32] Insulin resistance plays a central role in the development of type 2 diabetes, but the precise defects in insulin action remain to be elucidated. Glycogen synthase kinase 3 (GSK-3) can negatively regulate several aspects of insulin signaling, and elevated levels of GSK-3 have been reported in skeletal muscle from diabetic rodents and humans. Ring et *al.,* (2003) synthesized new class of highly selective GSK-3 inhibitors, aminopyridine derivatives 60-61 (Figure 14) that are effective at low nanomolar concentrations in enzyme assays and submicromolar concentrations in isolated cells and tissues. Aminopyridines 60-61 (CHIR 98014 and CHIR 99021) were tested against 20 protein kinases related to GSK-3 and showed >500-fold selectivity for GSK-3. They demonstrated that these compounds activate GS in cultured cells and in isolated type 1 diabetic rat skeletal muscle and enhance *in vivo* glucose disposal in rodent models of type 2 diabetes. Derivatives 60 and 61 were also very effective in inhibiting murine and rat GSK-3, with IC_{50} values of 6.4 and 7.4 nmol/l respectively.[33] Meijer et *al.,* (2004) mentioned 2-aminopyridine 62 as

GSK-3α inhibitor used to treat diabetes 2 with IC_{50} of 0.004 μM.[34]

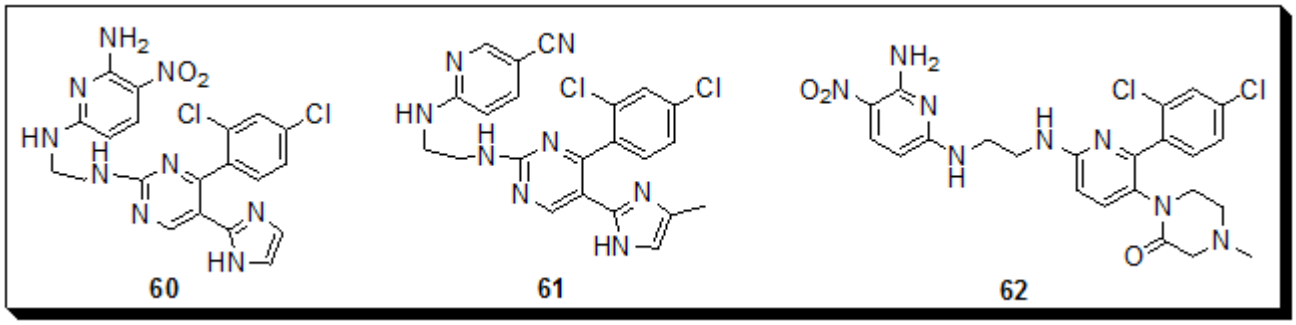


Figure 14
2-Aminopyridines 60-62 – antidiabetics

6.2-AMINOPYRIDINE AS ANTIMICROBIAL AGENT

In last decades, there has been a growing interest in synthesis, researching and developing new antimicrobial agents from various sources to combat microbial resistance.[35] Microbial resistance, to antibiotics is one of the most important global health problem, justifying the necessity of identifying innovative, radical antimicrobial agents. The antibiotic resistance problem is amplified by the ability of bacteria to grow in adherent state, developing microbial communities called biofilms, that exhibit a phenotypic resistance, i.e. tolerance, rendering them to 1000-fold more resistant to antibiotic treatments with respect to their planktonic counterparts.[36] Abdel-Aziz et *al*., (2005) synthesized a series a 2-aminopyridines starting from 2-alkoxypyridines *via* a Lewis acid-promoted transformation. The antibacterial screening of all compounds was performed against the Gram-positive *S. aureus*, Gram-negative *E. coli* and minimum inhibitory concentration (MIC) was determined for compounds along with ciprofloxacin as standard control. Amongst all the compounds tested, 63 and 64 (Figure 15) demonstrated the most potent antibacterial activity against both *S. aureus* (11, 7 μg/mL respectively) and *E. coli* (4.1, 3.2 μg/mL respectively).[37] El-Salam and Mohamed, (2005) synthesized a series of 4-substituted-N^1-2-pyridylsulfanilamides 65-66 and evaluated their antimicrobial activities against four bacteries: *S. aureus, P. aureginosa, B. subtilis, E. coli* using chloramphenicol as standard. All compounds show a remarkably qualitative activity against *B. subtilis*.[38] Starting from 2-aminopyridine, Salimon et *al*., (2011) synthesized acetohydrazide 68 *via* ethylaceto-acetate 67 and finnaly 1-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-(pyridine-2-ylamino)ethanone 69.

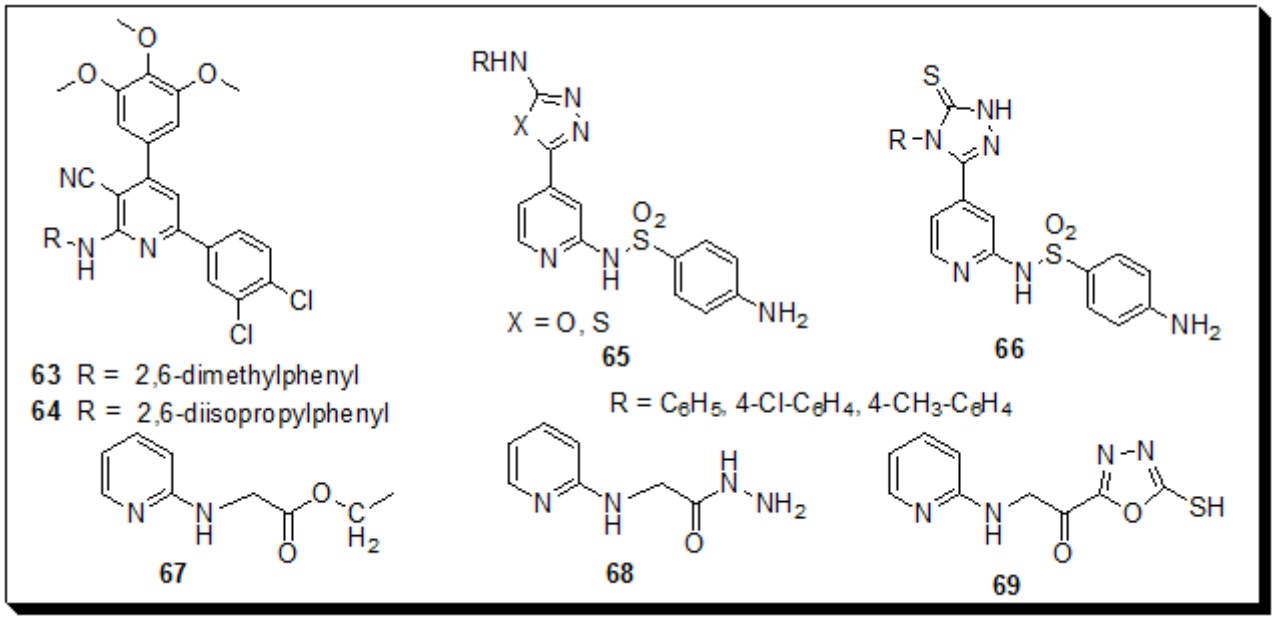


Figure 15
2-Aminopyridines 63-69 – antimicrobial agents

The antimicrobial activities of all compounds were tested against six pathogenic microorganisms *S. aureus*, *S. viridans*, *E. coli*, *F. oxysporum*, *A. alternata* and *A. solani*. For all compounds MIC was determinated. It was found that the presence of the 1,3,4-oxadiazole nucleus increased significant antimicrobial activity (MIC value for **69** ranging from 30.2 - 43.2 μg/ ml).[39] Patel et *al*., (2010) reported synthesis of 2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinic acid **70** and its hydrazide **71** (Figure 16) with good activity against four bacterial strains: *S. aureus, S. pyogenes, E. coli* and *P. aeruginosa* compared to ampicillin (MIC = 100 μg/mL for **70** against E. coli). Antifungal activity are moderate for all compounds against *A. niger* and *A. clavatus* and good

against *C. albicans.*[40] Kumar and Chaudhary, (2010) reported synthesis of a new 2-aminopyridine Schiff base ligand bis(2-(pyridin-2-ylimino)phenyl)-4,4'-(diazene-1,2-diyl)dibenzoate **72** and its metal complexes with divalent transition metal ions (Co, Ni, Cu, Zn) and screened their antimicrobial activities towards bacteria *S. aureus* and *E. coli* (MIC 3,7 µM against both strains for **72**) and antifungal activities towards fungi *A. niger* and *C. albicans* (MIC 7,5 µM against both strains for **72**). The complexes have higher antimicrobial activities than the ligand.[41] Patel and Shaikh, (2010) reported a new series of 2-amino-6-methylbenzothiazoles **73 a-h** and *in vitro* antimicrobial screening against *S aureus, S. pyogenes, E. coli* and *P. aeruginosa* bacteria and three fungal species *C. albicans, A. niger* and *A. clavatus.* Compound **73h** have best antimicrobial activity with MIC between 25-62.5 µg/ml much better than ampicillin as standard. Some of the compounds are comparable with standard drugs.[42] El-Zemity, (2011) synthesized a series of 2-amino-5-substituted-pyridines **74a-d** and evaluated against five plant pathogenic fungi: *Botrydiplodia spp. Alternaria tennis, Heleminthosporium turicum, Fusarium oxysporium* and *F. moniliform* and three phytopathogenic bacteria: *Erwinia amylovora*, *E. carotovora* sub sp. *carotovora*, and *E. carotovora* sub sp. *Atroseptica*. The unsubstituted 2-amino-pyridine derivatives as in compound **74a** exhibited a moderately fungitoxic effect against the tested fungi and was less toxic to F moniliform. The ED_{50}s were 230, 340, 520 590 and >800 mg/ml against *A. tennis F. oxysporum, Botryodiplodia* spp., *H. tursicum* and *F.moniliform*, respectively. Introducing the methyl group at position R_3 of the aromatic pyridine ring in **74b** improved the fungitoxic effect. Replacing the benzotriazole moiety in **74c** with thiophenol to give **75** tremendously increased the fungicidal activity against all tested fungi with ED_{50} values of 14, 21, 23, 27, and 29 mg/ml for *A. tennis, H. tursicum, Botryodiplodia* sp., *F. oxysporium* and *F. moniliform*, respectively. Compound **75** has shown high bactericidal activity. Its ED_{50} values were 310, 330 and 280 mg/ml against *E. amylovovera,*

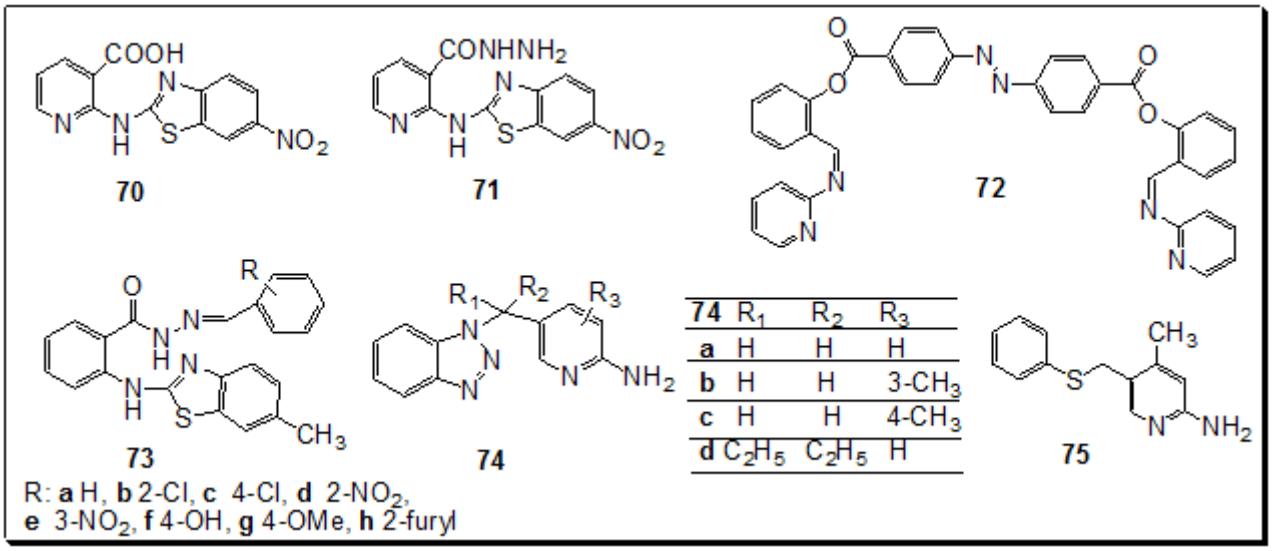


Figure 16
2-Aminopyridines 70-75 – antimicrobial agents

***E. carotovera* sub. *atroseptica* and *E. carotovera* sub sp. *carotovera*, respectively.**[43]

7. 2-AMINOPYRIDINE AS ANTIVIRAL AGENT

Herpes simplex virus (HSV)-1 and -2, varicella – zoster virus (VZV), Epstein–Barr virus (EBV) [HHV-4], Cytomegalovirus (CMV) are few of 80 known herpes viruses that cause infections humans.[44] Recent studies report that HSV infection rate has continuously increased in most countries. HSV causes a variety of diseases in humans in various stages, especially in immunocompromised patients. A normal sequela to a primary infection is the establishment of latency as the virus takes up permanent residence in the ganglia of the host. Nucleoside analogs, acyclovir, penciclovir, valaciclovir, famciclovir and ganciclovir have been approved for treatment of HSV infections.[45] Mibu et *al.*, (2007) synthesized *N*-monoacyl-2,6-diaminopyridines **76a-c** and *N*,*N*'-diacyl-2,6-diamino-pyridines **77a-c** (Figure 17) from 2,6-diaminopyridine by acylation with the corresponding acyl halide or by dehydration with the corresponding carboxylic acid using 1,3-dicyclohexylcarbodiimide (DCC). The antiviral activities of compounds were estimated using plaque reduction assay with HSV-1. All *N*-monoacyl-derivatives (**76a-c**) showed significant anti-herpes simplex virus (HSV)-1 activity (EC_{50} = 15.3—18.5 mg/ml). The CC_{50} values of **76a-c** measured using Vero cells ranged at 37.5—50.0 mg/ml. These compounds showed no significant antibacterial activities with *Escherichia coli* or *Staphylococcus aureus* even at a concentration of 1 mg/ml. The *N*,*N*'-diacyl derivatives **77a-c** showed no significant anti-HSV-1 activity.[46]

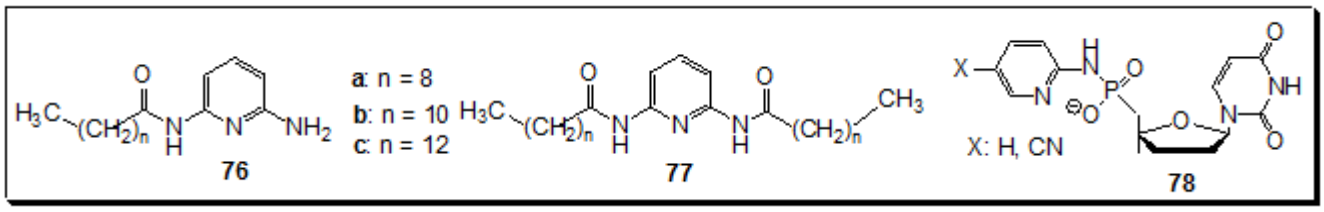


Figure 17
2-Aminopyridines 76-78 – antiviral agents

Human immunodeficiency virus (HIV)-1 is a unique invader of the immune system that leads to acquired immunodeficiency syndrome (AIDS) if not treated. HIV has affected over 71 million people around the world since its emergence. Unfortunately, there is no protective vaccine and the disease is not curable by the available therapeutic strategies.[47] Kolodziej et *al*, (2015) synthesized by condensation of nucleoside 5'-H-phosphonate with a 2-aminopyridine followed by oxidation new (N-heteroaryl)phosphoramidate derivatives 78 as potential anti-HIV therapeutics. All derivatives studied showed rather similar level of antiviral activity (EC_{50} ≈ 1.20 nM; EC_{90} ≈ 10-200 nM).[48]

8. 2-AMINOPYRIDINE AS ANALGESIC AND ANTI-INFLAMMATORY AGENT

The transient receptor potential vanilloid type 1 (TRPV1) is a cation channel protein, which contributes to inflammation, acute and persistent pain. Antagonists of human TRPV1 (hTRPV1) represent a novel therapeutic approach for the treatment of pain.[49] Ann et *al*, (2016) synthesized 2-aminopyridines 79a-g (Figure 18) in 4 steps starting from the commercially available 2-chloro-6-(trifluoromethyl)nicotinonitrile as potent TRPV1 antagonists. It was found that incorporation of hydrophobic groups on the nitrogen of the phenylsulfonamide, providing tertiary phenylsulfonamides (79b–79g), led to potent binding affinity and antagonism. The binding affinities (Table-4) increased with the size of the N-substituent: methyl (79b) < isopropyl (79c) < phenyl (79d) < 4-fluorophenyl (79e) < cyclohexylmethyl (79f) < benzyl (79g). Antagonism by the more potent compounds fell in the range of $K_{i(ant)}$ = 5–10 nM. The N-benzylphenylsulfonamide 79g exhibited high affinity and potent antagonism with K_i = 1.99 nM and $K_{i(ant)}$ = 5.9 nM, namely a 4-fold enhancement in binding affinity but a 2.5-fold reduction in antagonism compared to 79a. Compound 79g have excellent, dose-dependent analgesic efficacy 20–30 min after injection. The ED_{50} was 15.6 mg/kg.[50]

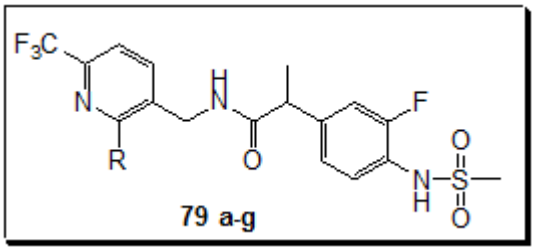
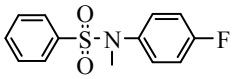
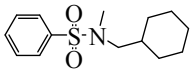
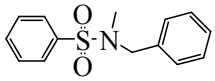


Figure 18
2-Aminopyridines 79a-g – analgesic and anti-inflammatory agents

Table 4
Binding affinity and antagonism of componds 79a-g

79	R	Binding affinity K_i(nM)	Antagonism K_i(nM)
a	4-Methylpiperidine	7.9(±1.6)	2.22(±0.47)
b	N-methylbenzenesulfonamide	698(±8.7)	100(±19)
c	N-isopropyl-benzenesulfonamide	410(±120)	27.6(±4.9)
d	N-phenylbenzenesulfonamide	18.3(±2.6)	6.0(±1.4)
e		7.3(±1.7)	11.8(±1.3)
f		230(±0.29)	10.0(±2.7)
g		1.99(±0.22)	5.9(±1.1)

9. 2-AMINOPYRIDINE AS CXCR1/2 INHIBITOR

Leukocyte trafficking into tissue sites of inflammation is directed by chemokines. Chemokines are grouped into four families based on a cysteine motif in the amino terminus of the protein (1, 2). Human CXC ligand 8 (CXCL8) and related molecules are polymorphonuclear

cells chemoattractants. Two high-affinity human CXCL8 receptors are known, CXC chemokine receptor 1 (CXCR1) and CXC chemokine receptor 2 (CXCR2).[51] Experiments with animals lacking CXCR1 and/or CXCR2 activity have demonstrated that their inhibition could be beneficial in the treatment of many diseases, including asthma, chronic obstructive pulmonary disease, and inflammatory bowel disease), cancer (melanoma, pancreatic, and colon cancer), Alzheimer's disease, and traumatic brain injury. Schuler et *al.*, (2015) synthesized a series of 2-aminopyridine-boronic acids **80** (Figure 19) and screened their activity against CXCR1 and CXCR2 (Table-5). Boronic acid **80a** have inhibitory activity at CXCR2. This compound also exhibited improved aqueous solubility, making it good scaffolds for further substitution. The addition of a phenyl ring in **80b** significantly improved potency of the inhibitor. The presence of a furan ring in **80c** determine similar potency to the phenyl compounds.[52]

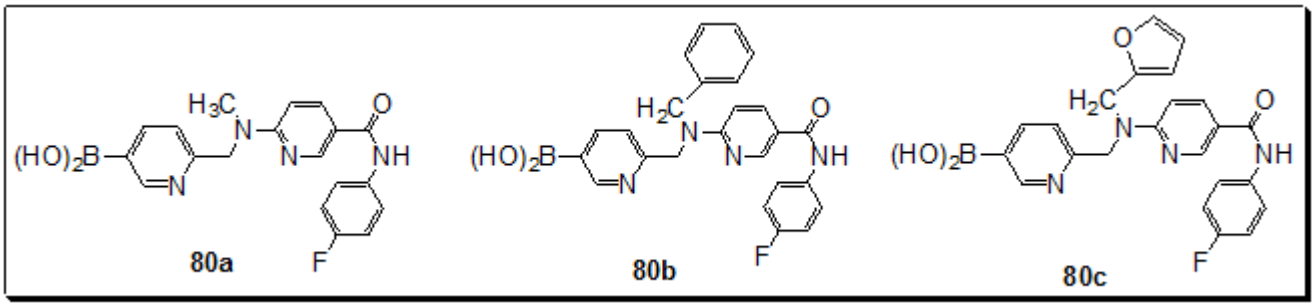


Figure 19
2-Aminopyridines 80a-c – CXCR1/2 inhibitor

Table 5
Inhibition of IL8-mediated intracellular calcium release in RBL cells stably transfected with CXCR1 or CXCR2

Compound	CXCR1 IC_{50}(nM)	CXCR2 IC_{50}(nM)
80a	1700±200	81±19
80b	326±39	298±45
80c	3.3±0.4	21±3

10. 2-AMINOPYRIDINE AS RENIN INHIBITOR

Renin is a particularly promising target for blood pressure, progression of cardiovascular and renal diseases because of the action of the aspartyl protease renin which is the rate-limiting initial step of the renin-angiotensin-aldosterone system. Starting from 2-chloro-6-methylnicotinic acid, Imaeda et *al.,* (2016) synthesized compound **82** *via* the intermediate **81** (Figure 20), and reported its renin inhibitory activity of IC_{50} = 38μM. X-ray crystallography study was carried out for **82** to understand the binding mode of it and determine an approach to increase renin inhibitory activity.[53]

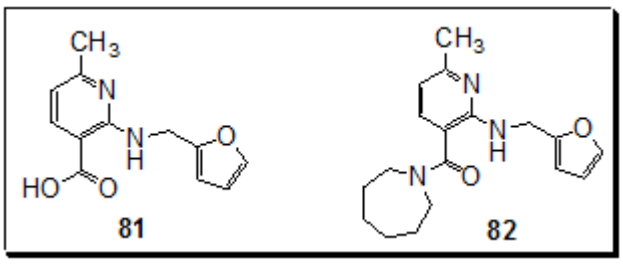


Figure 20
2-Aminopyridines 81-82 – Renin inhibitor

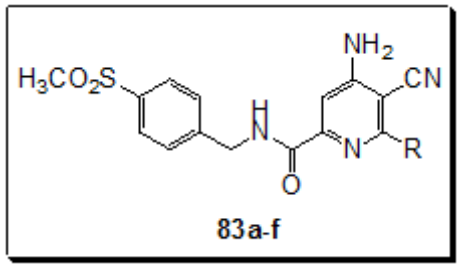
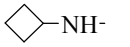
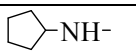


Figure 21
2-Aminopyridines 81-82 – JNK-1 inhibitor

11. 2-AMINOPYRIDINE AS JNK-1 INHIBITOR

JNKs (c-Jun N-terminal kinases) are important cell signaling enzymes. Three distinct genes: JNK-1, JNK-2 and JNK-3 are known and they are activated in response to various cytokines and cellular stresses such as heat shock, irradiation, hypoxia, chemotoxins and peroxides. JNK-1 which is a member of the mitogen activated protein kinase (MAP kinase) family of enzymes responsible for the serine/threonine phosphorylation of intracellular targets plays a central role in linking obesity and insulin resistance.[54] Yi et *al.*, (2006) reported the synthesis of a series of JNK-1 aminopyridine carboxamide inhibitors 83a-f (Figure 21) with their JNK-1 pIC_{50}s (-log IC_{50}) of inhibitors (Table-6).[55]

Table 6
JNK-1 pIC_{50} values of compounds 83a-f

Compound	R	pIC_{50}
83a		7.495
83b		7.071
83c		7.018
83d	C_6H_5-CH_2-NH-	6.086
83e	H_2N-CO-NH-CH_2-CH_2-NH-	7.032
83f	H_2N-CO-CH_2-CH_2-NH-	7.180

12. 2-AMINOPYRIDINE AS PKCθ INHIBITOR

Protein kinase C (PKC) is a family of serine- and threonine-specific protein kinases that can be activated by the second messenger diacylglycerol.[56] PKCθ plays a central role in the activation of T cells and integrates signals from both the T cell receptor (TCR) and the co-stimulatory CD28. It is anticipated that a selective PKCh inhibitor will provide the desired balance of efficacy and safety for the treatment of autoimmune diseases. Jimenez et *al.*, (2012) synthesized a novel series of 2-aminopyridines as PKCθ inhibitors 84-90 (Figure 22). Compound 84 was selected for in vivo assessment on the basis of its overall profile. Good PKCθ potency (K_i = 0.003 μM) translated to good cell activity (IL-2 IC_{50} 0.052 μM) and excellent overall kinase selectivity. Compound 84 was dosed once orally at 25, 50 and 100 mg/kg in tested mouse SEB-IL2. The data showed that 84 significantly inhibited the production of IL-2 in a dose dependent manner. The level of efficacy observed *in vivo* is in line with the free concentration (FC) achieved at the doses tested (at 100 mg/kg C-max FC is 150 nM).[57]

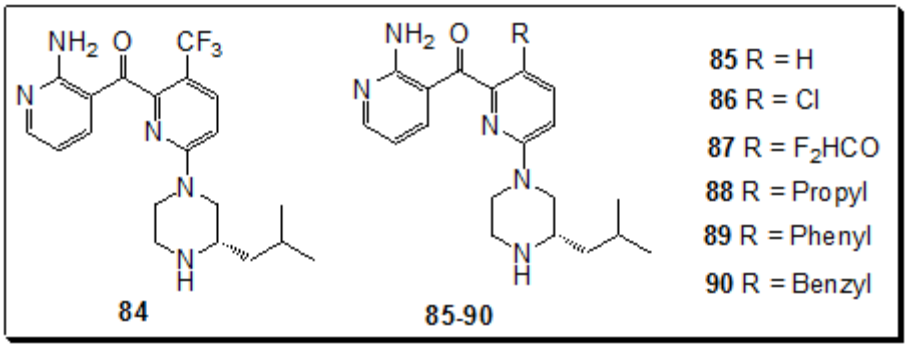


Figure 22
2-Aminopyridines 84-90 – PKCθ inhibitor

13. 2-AMINOPYRIDINE AS SYK INHIBITOR

Syk (spleen tyrosine kinase) is a cytoplasmic protein with central role in the immune system for its ability to couple immune cell receptors to intracellular signaling pathways that regulate cellular responses to extracellular antigens and antigen-immunoglobulin complexes of special importance to the initiation of inflammatory responses. Therefore, Syk is an attractive target for therapeutic kinase inhibitors to treat acute and chronic inflammation. Recently was recognized its role as a promoter of cell survival in numerous cancer cell types ranging from leukemia to retinoblastoma that attracted considerable interest as a target for a new generation of anticancer drugs.[58] Castillo et *al*, (2012) synthesized a series of 2-aminopyridines 91-95 (Figure 23) *via* Suzuki-type coupling reaction and determined their Syk IC_{50} values. For highly potent aminopyridine 91 bearing a 4-trifluoromethyl-2-pyridyl motif was determined a IC_{50} subnanomolar value of 0.6 nM. The presence of amine group at in compound 93 (IC_{50} 4) resulted in more than 10-fold increase in enzymatic potency compared to compound 92 (IC_{50} 62). Presence of methyl or benzyl group in 94 and 95 did not affect considerable Syk enzymatic potency compared to 93 (IC_{50} 4 for 94 and IC_{50} 8 for 95).[59]

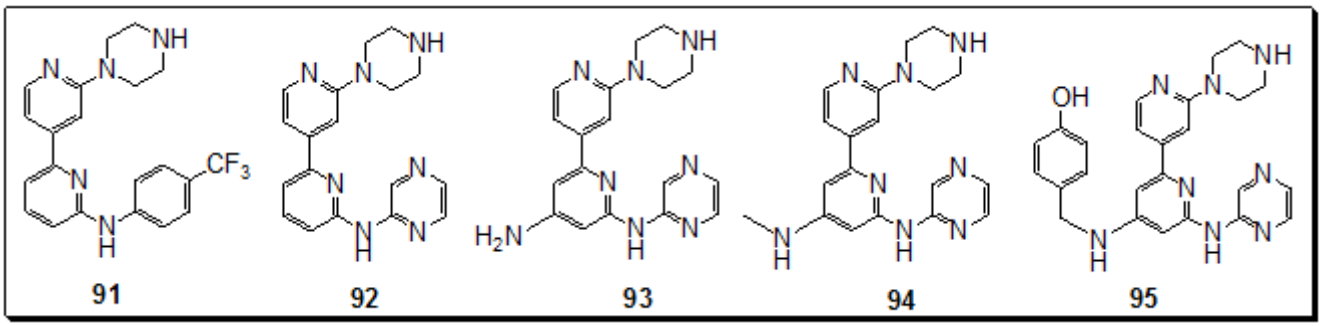


Figure 23
2-Aminopyridines 84-90 – Syk inhibitor

14. 2-AMINOPYRIDINE AS ANTIPARASITIC AGENT

Sleeping sickness or Human African Trypanosomiasis (HAT) is endemic in about 35 African countries and around 70 million people are in danger being infected with *Trypanosoma brucei. T. brucei* is transmitted through the bite of infected blood feeding tsetse flies from the *Glossina* genus. Therapeutic strategies for this neglected tropical disease suffer from disadvantages such as toxicity, high cost, and emerging resistance. Valenciano et *al.*, (2016) found 2-aminopyridine 96 (Figure 24) as the most promising compound with potent antiparasitic activity (IC_{50} = 120 nM). Also, it was shown that 96 is a selective inhibitor of an essential gene product, *T. brucei* extracellular signal-regulated kinase 8 (TbERK8). Compound 96 has a K_i of 1.25 μM for TbERK8 and demonstrate its utility in establishing TbERK8 as a potentially druggable target in *T. brucei*.[60]

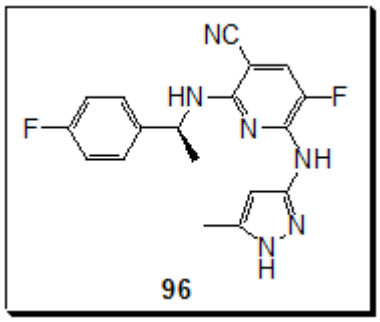


Figure 24
2-Aminopyridine 96 - Antiparasitic

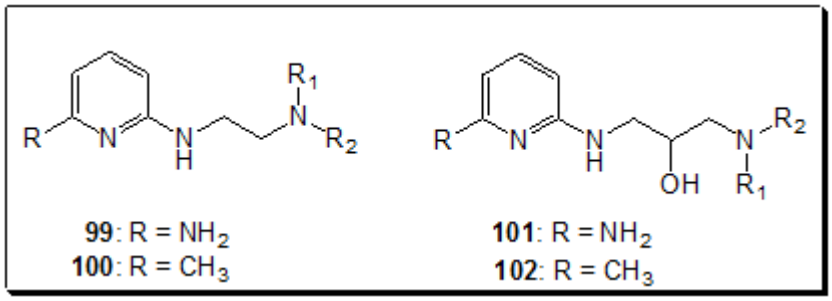


Figure 26
2-Aminopyridines 99-10 2- **Anticonvulsant, cardiac and antihistaminic**

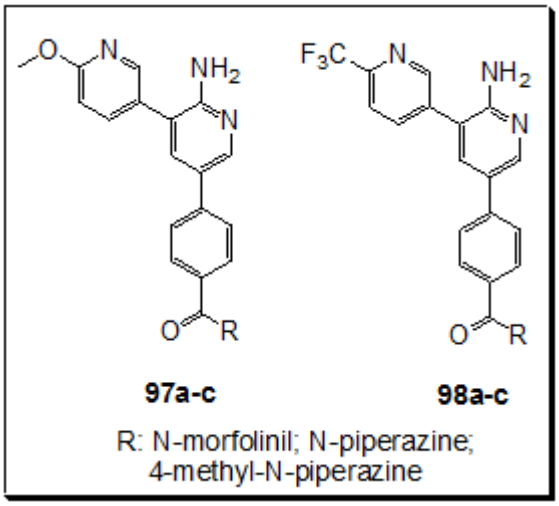


Figure 25
2-Aminopyridines 97-98 –Antimalarial agents

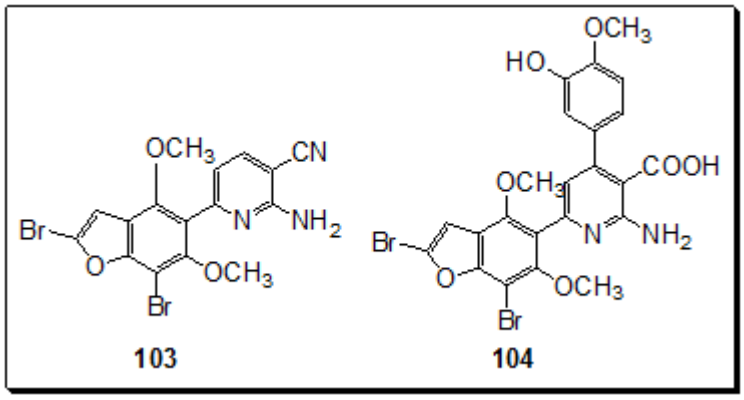


Figure 27
2-Aminopyridines103-104 –Antitumoral and antimicrobial

15. 2-AMINOPYRIDINE AS ANTIMALARIAL AGENT

Malaria, an infectious disease caused predominantly by the *Plasmodium falciparum*, is widely spread in Asia, Africa and Latin America. Malaria is treated with specific drugs depending on the type and severity of the disease, but more therapies applied nowadays are from decades ago. There is a human and economic necessity to discover new antimalarial drugs and to establish new strategies for treat this parasitic disease that causes hundreds of thousand of deaths annual.[61] Cabrera et *al.*, (2012) synthesized new 3,5-diaryl-2-aminopyridines **97a-c** and **98a-c** (Figure 25) which demonstrated promising *in vivo* efficacy in the *Plasmodium berghei* mouse model and will be evaluated *in vivo* as clinical drugs on humans. Also, these compounds were potent hERG channel inhibitors.[62]

16. MISCELLANOUS ACTIVE 2-AMINOPYRIDINE

Ravlee et *al.,* (2003) reported the synthesis of a series of 2-aminopyridines 99-102 (Figure 26) with anticonvulsant, cardiac and antihistaminic activities. Also, the biological activities were correlated with the structure of the compounds (SAR studies). All the compounds exhibited significant anticonvulsant activity. The amphetamine antagonism of the compounds was reported for all synthesized compounds. The percentage reduction of motor activity by the compounds was between 11.36% and 96.28% and ED_{50} values of 41.9 (best activity for 102: R_1: phenyl, R_2: hydroxy)-145 mg/Kg. It has been hypothesized that the mechanism of action of anticonvulsants is achieved by blocking Ca^{2+} channels. Only the water-soluble compounds were tested for their cardiac activity *in vivo* (wistar albino mice and hartely guinea pig). Only compounds 100 and 102 exhibited potential cardiac activity. Of all the compounds, the most active were found those that

contain a tertiary amine. The presence of 4-hydroxyphenyl amino-group lead to the best cardiac activity of all secondary amines. Also, the compounds exhibited significant sympatholytic action, at administration concurrently with adrenaline. It was found that the piperazino-, dietylamino-, diphenylamino-ethane derivatives 99-100 showed good antihistaminic activity, while the propane derivatives 101-102 were inactive.[63] El-Nakkady et *al.*, (2012) synthesized of benzofuranes bearing 2-aminopyridine 101-102 and reported their antimicrobial activity against *Staphylococcus aureus* ATCC 6538, *Staph. epidermidis* ATCC12228, *Escherichia coli* ATCC8739, *Klebsiella pneumonia* ATCC4352, *Salmonella typhi, Shigella flexneri* and *Candida albicans* ATCC10231. Compound 103 (Figure 27) have antibacterial activity against all tested strains with a mean zone of inhibition equal to 19.5 (0.521 μM). The cytotoxic activity of newly synthesized derivatives was screened on liver carcinoma cell line (HEPG2) in comparison to the traditional anticancer drugs: 5-FU and DOX. Compound 104 was one of the most active of all compounds and induced growth inhibition in a dose-dependent manner against HEPG2 when compared with 5-FU and DOX (IC_{50} = 0.0061μM while for 5-FU and DOX were 0.0384 and 0.00654 μM) while 103 have IC_{50} = 0.0114μM.[64] On the basis of classic antidiabetic drug, 2-aminopyridine derivative, rosiglitazone 105 (Figure 28), novel thiazinanone analogs were synthesized and evaluated as potential antidyslipidemic and antihyperglycemic agents 106.[65-66]

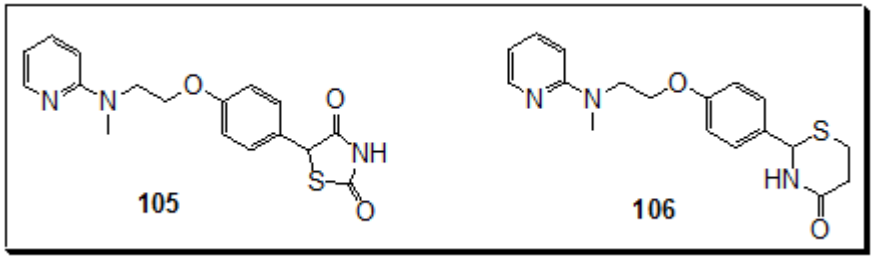


Figure 28
2-Aminopyridines 105-106 – Antidyslipidemic and antihyperglycemic agents

CONCLUSION

This study reveal that the 2-aminopyridine based compounds have a broad range of medicinal properties, even if it is a simpler structure without any other hetero-ring in molecule, or is a more complex molecule with more hetero-rings. 2-Aminopyridines can be very good drugs for treating several diseases highlighted in this review. This pharmacophore is present in compounds that posses different biological properties, like antitumoral, anti-Alzheimer, NOS inhibitors, renin inhibitors, antidiabetic, antiviral, antimalarial, antimicrobial compounds, etc. So, older and most recent researches have indicated that field of 2-aminopyridines is desirable to intensify due to the encouraging results obtained on a wide range of compounds with medicinal properties.

CONFLICT OF INTEREST

Conflict of interest declared none.

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Reviewers of this article

Professor Dr. Chem. Ana Emandi

UNIVERSITY OF BUCHAREST
FACULTY OF CHIMISTRY
DEPARTMENT OF INORGANIC CHEMISTRY
90-92 SOSEAUA PANDURI, DISTRICT 5,
BUCHAREST, ROMANIA

Prof.Dr.Prapurna Chandra Rao

Affiliation
Assistant Proffessor, KLE University,
Belgaum, Karnataka

Prof.Dr.K.Suriaprabha

Asst. Editor , International Journal of Pharma and Bio sciences.

Prof.P.Muthuprasanna

Managing Editor , International Journal of Pharma and Bio sciences.

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