JChrDD | Vol 2 | Issue 2 | 2011: 71-78
ISSN 2249-6785
Journal of Chronotherapy and Drug Delivery

Received: Nov 29, 2010
Revised: Dec 25, 2010
Accepted: Jan 6, 2011

Review

PYRIDINE: POTENTIAL FOR BIOLOGICAL ACTIVITIES

Sachin Kumar*, Pramod Kumar Sharma, Rupesh Dudhe, Nitin Kumar

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology,

NH-58, Baghpat By-pass Crossing, Delhi-Haridwar Highway, Meerut-250005 (India)

* Corresponding author. Tel: +91-09412131371

E mail: kumarsachin122@gmail.com

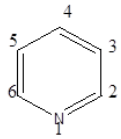
Abstract

The objective of medicinal chemistry is design and production of compounds that can be used as medicine for the prevention, treatment and cure of humans or animal diseases. It is concerned with the invention, discovery, design and identification of biologically active compounds, the study of their metabolism, interpretation of their mode of action at the molecular level and the construction of structure activity relationship (SAR), the relationship between chemical structure and pharmacological activity for a series of derivatives have been synthesized as target structures and evaluated for their biological activities. Amongst the wide range of pharmacologically active heterocyclic pyridines and some other pyridine fused ring systems have concerned great awareness as prospective chemotherapeutic agents. Since pyridine derivatives continue to be a focus for great concern due to the wide variety of biological activities, therefore they are generally screened for large number of activities such as anticancer, analgesic, antimicrobial, antiviral, antiulcer activities.

Key Words: Pyridine, Heterocyclic, Biological activity, Chemotherapeutic agents

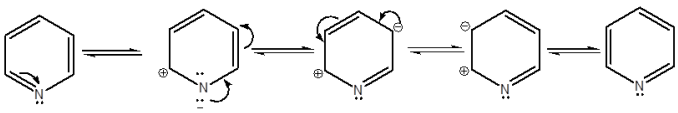
Introduction

Pyridine is a six member heterocyclic compound composed of five carbon atoms and one nitrogen atom.



In pyridine all ring atoms, five carbons one nitrogen atoms, are sp2 hybridized. Two of the sp2 orbital's on each atom overlap with each other to form the C-C and C-N σ bond. The third sp2 orbital on each carbon atom overlaps with s orbital from hydrogen to form the C-H σ bonds; the third sp2 orbital on nitrogen is occupied by the nitrogen lone pair electrons. All σ bonds in pyridine lie in one plane.

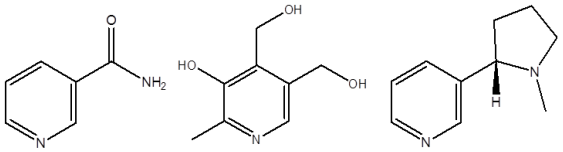
Pyridine shows some aromatic properties because the resulting molecular orbital satisfies the Huckel's rule (n= 1 in 4n+2), according to the resonance theory pyridine is considered to be hybrid of the following five contributing structures.



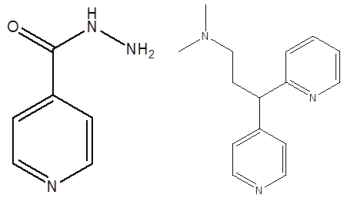
The nitrogen atom on pyridine features a basic loan pair of electrons. Because this lone pair is not delocalized into the aromatic π-system, pyridine is basic with chemical properties similar to tertiary amines. Pyridine is protonated by reaction with acids and forms a positively charged aromatic polyatomic atom called pyridinium. In organic reactions pyridine behaves both as a tertiary amine,

undergoing protonation, alkylation, acylation and N-oxidation at nitrogen and as an aromatic compound, undergoing nucleophillic substitution. It is easily susceptible to alkylating agents to give N-alkylpyridinium salts.

Physically C_5H_5N Organic base; flammable, toxic yellowish liquid, with penetrating aroma and burning taste; soluble in water, alcohol, ether, benzene, and fatty oils; boils at 116 °C. In many enzymes, the prosthetic pyridine nucleotide (NADP) is involved in various reduction-oxidation reactions, pyridine in biological systems is its presence in the vitamins niacin (1) and pyridoxine (2) (vitamin B6) but also in highly toxic alkaloids such as nicotine (3).[1] Pyridines find omnipresent applications in medicaments and in agrochemicals.[2] The leading group are antimicrobials (isoniazid, (4)) and histamine h1 antagonists such as pheniramine (5), but also anticancer, analgesic, and antidepressant agents. Pyridine derivatives continue to attract great interest due to the wide variety of interesting biological activities observed for these compounds, such as anticancer, analgesic, antimicrobial, and antidepressant, activities. Pyridine is used in the pharmaceutical industry as a raw material for various drugs, vitamins, and fungicides and as a solvent [3-6].



(1) (2) (3)

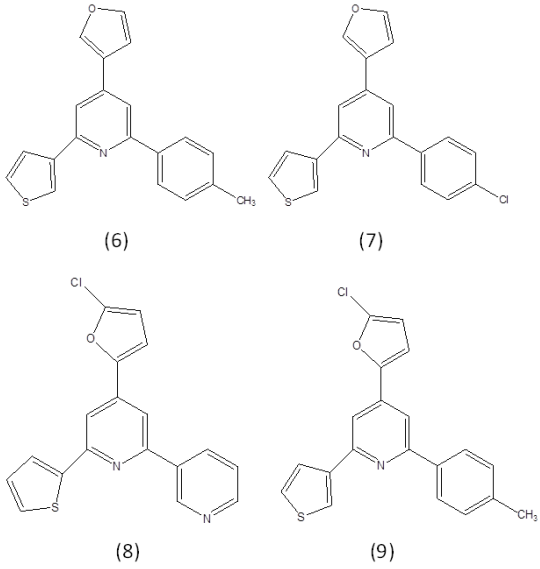


(4) (5)

Biological activities of pyridine ring derivatives

Anticancer activity

Lee et al synthesized a series of 2-(thienyl-2-yl or -3-yl)-4-furyl-6-aryl pyridine derivatives and evaluated for their topoisomerase I and II inhibition and cytotoxic activity against human cancer cell lines. Compounds were showed moderate topoisomerase I and II inhibitory activity and showed significant topoisomerase II inhibitory activity. Most significant cytotoxicity against Hela, K562, HCT15, and MCF-7 cell lines, was shown by the compounds 6, 7, 8, and 9 respectively as compared to standard.[7]



(6) (7) (8) (9)

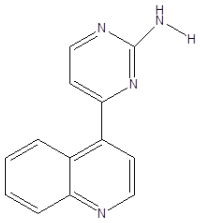
Angel, et al synthesized a series of 2-methylimidazo [1, 2-a] pyridine-derivatives, and evaluate the isosteric substitution of the 2-methylimidazo [1, 2-a] pyridin-3-yl scaffold by quinolin-4-yl or quinolin-3-yl moieties. Since the Quinolin-4-yl-substituted compounds contributed as a lead of cytotoxic and CDK inhibitor compounds because, Quinolin-4-yl-substituted compound 10, showed significant cytotoxic activity and was most effective and selective against CDK1/cyca than against CDK2/cycb.[8]

Onnis et al synthesized and evaluated the anticancer activity of 2 arylamino-6-trifluoromethyl-3-(hydrazonocarbonyl) pyridines. The potent compound was 2, 6-dichlorobenzaldehydehydrazone (11), which inhibited the growth of all tested cancer cell lines with nanomolar potency, without having any animal toxicity.[9]

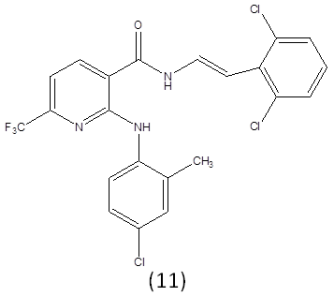
Shi et al chemo selectively synthesized thiazolo [3, 2-a] pyridine derivatives and screened for cytotoxicity to carcinoma HCT-116 cells and mice lymphocytes. Since, only thiazolo [3, 2-a] pyridine derivative (12), gave cytotoxicity selective to tumor cell line HCT-116 cells without evident side effects.[10]

Ahmeda et al prepared a series of pyridin-2-one, pyridin-2(1H)-thione derivatives and evaluated them against four human cancer cell lines (HepG2,

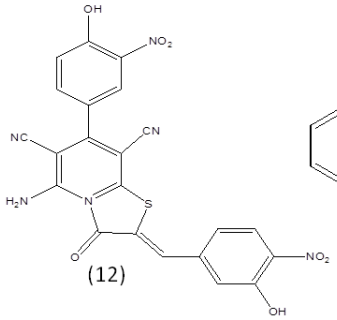
MCF7, HCT116, and HeLa. Compound 13 was found to be potent against hepatocellular carcinoma cell line (HepG2).[11]



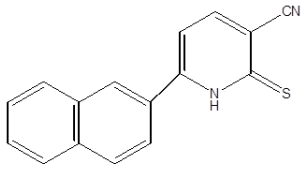
(10)



(11)

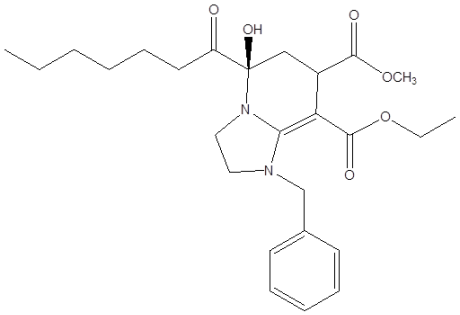


(12)



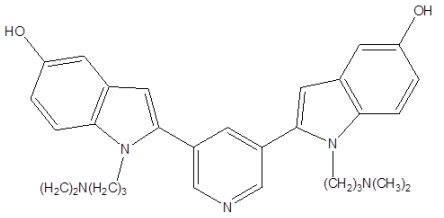
(13)

Rether et al prepared Novel hexahydroimidazo [1, 2-a] pyridines to fungal metabolite podoscyphic acid and its ester were evaluated to inhibit the TNF-α promoter activity in T-cells. They were found that the methyl ester (14) was most potent to inhibit the TNF-α gene expression in jurkat T-cells, and also inhibit the inducible TNF-α production in the myelomonocytic U937 cells with a 4.6μm IC50-value.[12]

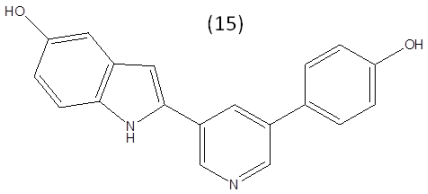


(14)

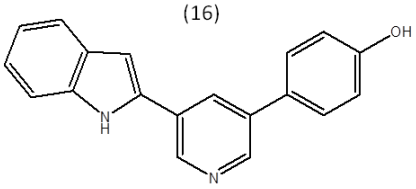
Jacquemard et al have synthesized and biologically evaluated a novel series of mono- and bis-indole-pyridine derivatives, (3, 5-bis (2-indolyl) pyridine and 3-[(2-indolyl)-5-phenyl] pyridine). Two major conclusions were drawn from their studies; first, a number of DNA-binding ligands were identified, in terms of DNA recognition, the most interesting molecule was compound 15, which behaves as a schematic DNA minor groove binder. Second, they were identified and characterized three CDK1 inhibitors: 16, 17, and 18, which exhibited selectivity over GSK-3.[13]



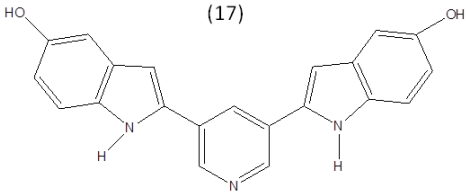
(15)



(16)

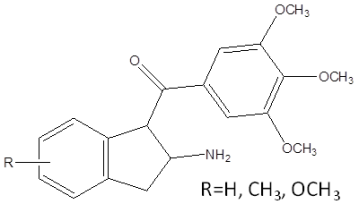


(17)



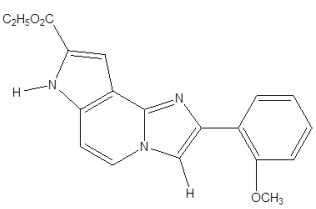
(18)

Romagnoli et al synthesized and evaluated a new series of tubulin polymerization inhibitors based on the 2-amino-3-(3, 4, 5-trimethoxybenzoyl) - 4,5,6,7 tetrahydrothieno pyridine molecular skeleton.[14] The most potential compound in present series was 2-amino -3- (3, 4, 5- trimethoxybenzoyl) -6-methoxycarbonyl- 4, 5, 6, 7- tetrahydrothieno [b] pyridine. In this series of N6-carbamate derivatives, any increase in the length and in the size of the alkyl chain resulted in reduced activity. The trimethoxybenzoyl moiety was crucial for retaining potency in this and other series of molecules which occupy the colchicines site. During the synthesis of new antitubulin agents, they have previously reported the potent *in vitro* antitumor activity of a series with general structure 19, characterized by the presence of a 2- amino- 3- (3, 4, 5-trimethoxybenzoyl)- benzo [b] thiophene skeleton.[15,16]

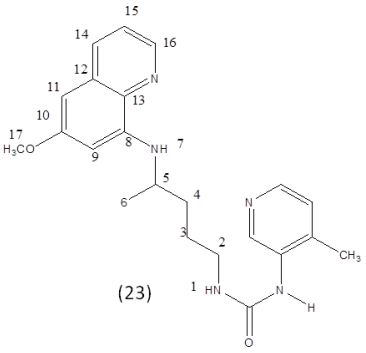


(19)

Son et al synthesized 2,6-diaryl-substituted pyridine derivatives bearing three aryl groups, which are the bioisosteres of terpyridine, for the development of novel antitumor agents and evaluated for antitumor cytotoxicity on SK-OV-3 (human ovary adenocarcinoma A549 (human lung carcinoma), HCT15 (human colon adenocarcinoma SK-MEL-2 (human malignant melanoma). From the SAR studies it was concluded that the number of aryl groups would be vital for their biological activities.[17]

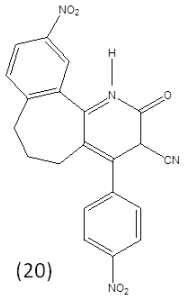


(22)

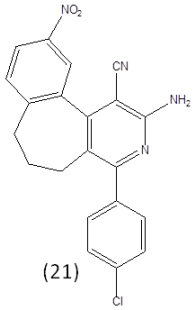


(23)

Amr et al synthesized and evaluated the antitumor activities of compounds utilizing 59 different human tumor cell lines, representing leukemia, melanoma, lung, colon, brain, ovary, breast, prostate and kidney. In the proposed work it was suggested that the anticancer property is due to the presence of nitrogen heterocyclic rings and the difference in activity is due to the various substituents in the phenyl group of the molecule. Especially, compounds especially 20, 21 had very potent *in vitro* antitumor activities at low concentration (log10 GI50 = 4.7) against the human tumor cell line.[18]



(20)



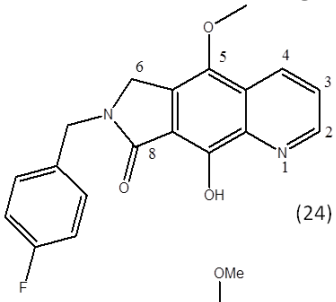
(21)

Antiviral activity

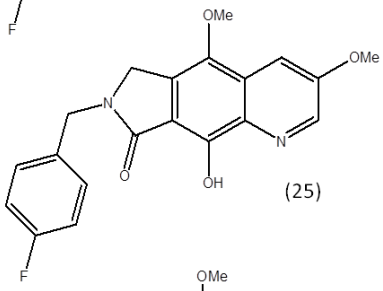
Chezal et al synthesized a series of imidazo [1,2-a] pyrrolo [2,3-c] pyridines and evaluated their anti-BVDV (bovine viral diarrhea virus) activities. From SAR studies, modifications at positions C-2 and C-3 imidazole moiety at the N-7 and C-8 pyrrole positions (compound 22) exhibited significant anti-BVDV activities, while substitution at the C-3 position decreased the antiviral potency.[19]

Zimbeg et al synthesized urea primaquine derivatives and evaluated the cytotoxic activities against colon carcinoma, human T-lymphocyte and murine leukemia. The most potent compound in the series was the pyridine and phenethyl derivative of urea (23) and exhibited selective inhibition against cytomegalovirus.[20]

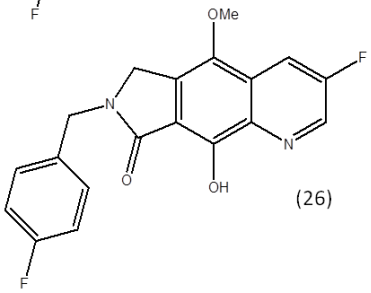
Metobo et al synthesized and evaluated a novel class of HIV-1 integrase inhibitors.[21] The presence of the pyridine was confirmed as the optimum for antiviral activity. The effect of substitution at 3-quinoline position (C3) position of the pyridine moiety (24) revealed interesting results. Methoxy substitution at C3 (25) largely sealed the enzymatic activity while humanizing anti-HIV potency in the cell assay. The pKa of the pyridine nitrogen and phenol which embrace the binding pattern is altered in analogs 25 and 26, showed change of activity.



(24)

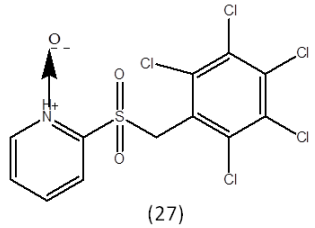


(25)



(26)

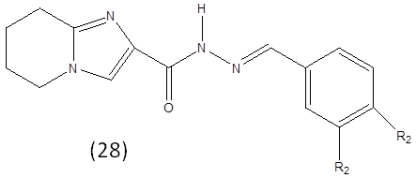
Stevens et al screened the anti-HIV activity of Pyridine-N-oxide derivatives and demonstrated that the prototype JPL-32 (27) which inhibits HIV-1 replication, also an efficient inhibitor of TNF-a-induced HIV-1 expression.[22]



(27)

Antimicrobial activity

Zdemir et al synthesized and evaluated eight new derivatives of tetrahydroimidazo [1, 2-a] pyridine (28a-h) for their antifungal effects against a group of *Candida* species (*Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Candida utilis*, and *Candida zeylanoides*) using agar diffusion and broth micro dilution assays. The MIC values were found to be in the range of 0.016–1 mg/mL.[23]



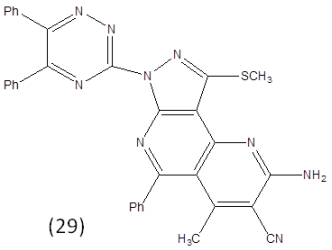
(28)

Compound	R_1	R_2
28a	H	CH_3
28b	H	$N(CH_3)_2$
28c	H	$CH(CH_3)_2$
28d	O-CH_2-O	
28e	H	NO_2
28f	H	Br
28g	H	Cl
28h	H	CN

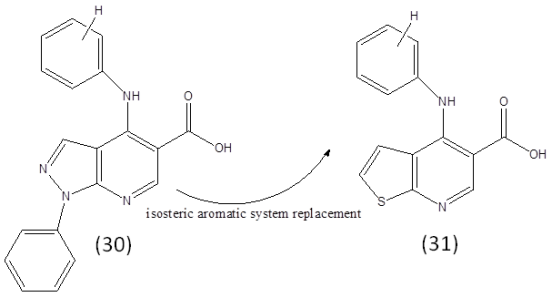
Siddiqi et al synthesized and evaluated antimicrobial agents against *Escherichia coli* (K-12), *Bacillus subtilis* (MTCC-121), *Staphylococcus aureus* (IOA-SA-22), *Salmonella typhymurium* (MTCC-98), *Candida albicans*, with ternary complexes [Fe(dipic)(4-picoline)]Cl, [M(dipic)(4-picoline)] [M ¼ Co or Ni] and [Cu(dipic)(4-picoline)]n of pyridine-2, 6-dicarboxylate dianion. The iron, copper and cobalt complexes showed significant antibacterial and antifungal activities.[24]

Ali et al synthesized a series of pyrazolo [3, 4-b] pyridine compounds and evaluated their antibacterial and antifungal activities. Compound 29 showed maximum activity analogous to the standard drugs with lower toxicity.[25]

Afonso et al evaluated a series of 4-(aryl amino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5- carboxylic acids (30a-m) and compared them with a new isosteric ring nucleus series, 4-(aryl amino) thieno[2,3-b] pyridine-5-carboxylic acids derivatives (31a-m). The results revealed significant antibacterial activity against drug-resistant *S. epidermidis* by 1 H- pyrazolo [3,4-b] pyridine derivatives. The structure activity relationship (SAR) study clearly showed that the position of functional groups has a great bang on the activity. Active derivatives of series 30 were subjected to *in silico* ADMET screening, which confirmed potential antibacterial property.[26]



(29)

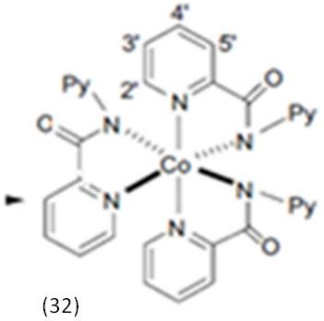


(30) (31)

Compound	R	Compound	R
30	H	31	H
30a	m-OCH_3	31a	m-OCH_3
30b	m-CH_3	31b	m-CH_3
30c	m-Cl	31c	m-F
30d	m-NO_2	31d	m-Br
30e	m-F	31e	m-F
30f	m-Br	31f	m-Br
30g	p-OCH_3	31g	p-OCH_3
30h	p-CH_3	31h	p-CH_3
30i	p-Cl	31i	p-Cl
30j	p-NO_2	31l	p-F
30l	p-F	31m	p-Br
30m	p-Br		

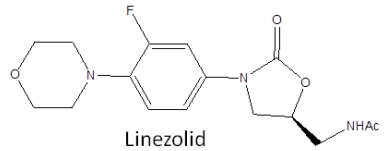
Mishra et al synthesized stable cobalt (III) compounds [Co(L1-3)3] and Na[Co(L4-6)2] from mono- and di-deprotonated ligands 2-(N-(X-pyridyl) carbamoyl pyridine (X ¼ 2, 3 or 4 for HL1-HL3, respectively) and 2,6-bis(N-(Y pyridyl) carbamoyl pyridine (Y ¼ 2, 3 or 4 for H2L4-H2L6, respectively) and screened for *in vitro* antimicrobial activity against isolated resistant strains of *Pseudomonas*, *Proteus*, *Escherichia coli* and

standard strains of *Pseudomonas aeruginosa* (MTCC 1688), *Shigella flexneri* (MTCC 1457) and *Klebsiella planticola* (MTCC 2272). The complexes [Co (L1)3] and Na [Co (L4)2] (32) had persuasive activity against standard and pathogenic resistant bacteria.[27]

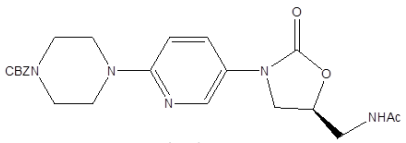


(32)

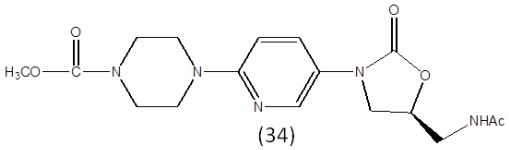
Cui et al synthesized a series of substituted piperazinyl pyridyl oxazolidinone compounds and evaluated them against Gram+ve organisms (Staphylococci, Streptococci, Enterococci). The Compounds 33 and 34 were found to be better to linezolid.[28]



Linezolid



(33)

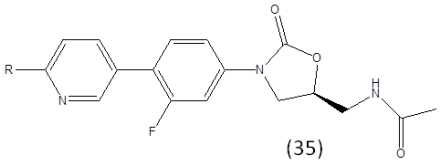


(34)

Weon Bin Im et al synthesized a series of substituted pyridine moiety of oxazolidinone derivatives and evaluated their antibacterial activity against four strains of Gram+ve organisms including drug resistant strains and two Gram-ve strains. The most potent compounds, 35b, 35e, and 35f were active against resistant Gram+ve organisms, *M. catarrhlis* and *H. Influenza*.[29]

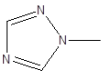
Analgesic activity

Hoonoor et al synthesized pyridine-2-ethyl-(3-carboxylideneamino) -3- (2- phenyl) -1, 2-dihydroquinazolin - 4 (3H)-one (36) coordinated metal complex, and characterized by single crystal X-ray diffraction studies. The analgesic activity was determined by acetic acid-induced writhing test in mice. They demonstrated the copper complex (36) showed significant dose-dependent inhibition mediated by inhibition of peripheral mechanisms of nociception .[30]

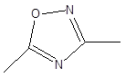


(35)

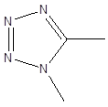
35b R =

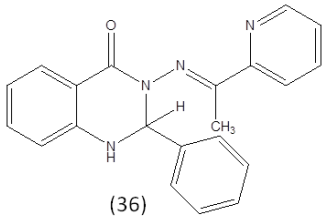


35e R =



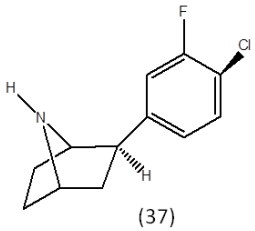
35f R =





(36)

Galya et al pharmacologically screened the selectivity and efficacy of 3-fluro substitution in the pyridine ring of epibatidine (37), which confirmed an increased efficacy and selectivity for α4β2 versus α3β4 nAChRs.[31]

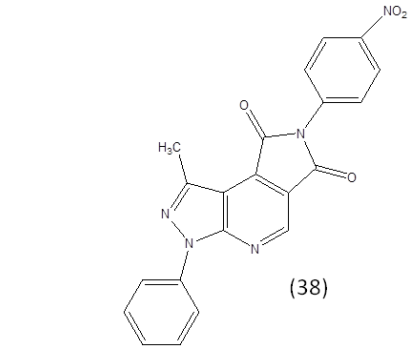


(37)

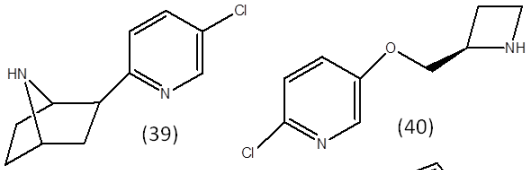
Menegatti et al synthesized four novel pyrazolo [3, 4-b] pyrrolo [3, 4-d] pyridine derivatives from the lead compound zolpidem. The potent central acting analgesic archetype compound LASS Bio- 873 (38) was obtained by isosteric modulation on the lead and the activity of resulted compound was reliant on the modulation of opioid receptors.[32]

Baraznenok et al synthesized some new compounds analogous to epibatidine (39) and tebanicline (ABT-594, 40) and evaluated the analgesic activity in mouse. The R isomer of

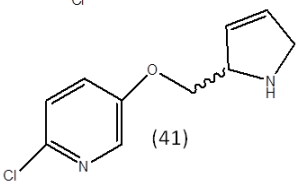
compound 41 gave useful results indicating that R-5 has favorable analgesic properties.[33]



(38)



(39) (40)



(41)

Conclusion

Pyridine is a unique compound associated with several biological activities. This article highlighted the work of many researchers regarding different pharmacological activities on pyridine derivatives. The review has presented comprehensive details of pyridine analogues, potent compounds reported for particular pharmacological activity.

Acknowledgement

The authors are thankful to Chairman, MIET, Meerut, for providing the necessary library and internet facilities.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

References

1. Henry GD. Tetrahedron. 2004; 60:6043-6061.
2. Tomlin C. The Pesticide Manual. 10th ed. Cambridge: British Crop Protection Council/Royal Society of Medicine; 1994.
3. Amr AG, Mohamed AM, Mohamed SF, Abdel-Hafez NA, Hammam AG. Bio Med Chem. 2006; 14: 5481–5488.
4. Bart A, Jansen J, Zwan JV, Dulk H, Brouwer J, Reedijk J. J Med Chem. 2001; 44: 245-249.
5. Shinkai H, Ito T, Iida T, Kitao Y, Yamada H, Uchida I. J Med Chem. 2000; 43:4667-4677.
6. Klimesˇova V, Svoboda M, Waisser K, Pour M, Kaustova J.1999; 54: 666–672.
7. Thapa P, Karki R, Choi H, Choi JH, Yun M, Jeong BS, Jung MJ, Namb JM, Na Y, Cho WJ, Kwon Y, Lee ES. J Bio Med Chem. 2010; 18: 2245–2254.
8. Vilchis-Reyes MA, Zentella A, Martı´nez-Urbina MA, Guzma´n A, Vargas O, Ramı´rez Apan MT, Gallegos JLV, Dı´az E. Eur J Med Chem. 2010; 45: 379–386.
9. Onnis V, Cocco MT, Fadda R, Congiu C. Bio Med Chem. 2009; 17: 6158–6165.
10. Shi F, Li C, Xia M, Miao K, Zhao Y, Tu S, Zheng W, Zhang G, Maa N. Bio Med Chem. 2009; 19: 5565–5568.
11. Ahmeda OM, Mohamed MA, Ahmed RR, Ahmed SA. Eur J Med Chem. 2009; 44: 3519-3523.
12. Rether J, Erkel G, Anke T, Bajtnerb J, Sternerb O. Bio Med Chem. 2008 ;16: 1236–1241.
13. Jacquemard U, Dias N, Lansiaux A, Bailly C, Loge C, Robert JM, Lozach O, Meijer L, Me´roura JY, Routiera S. Bio Med Chem. 2008; 16: 4932–4953.
14. Romagnoli R, Baraldi PG, Carrion MD, Lopez CO, Cara C, Preti D, Fruttarolo F, Pavani MG, Tabrizi MA, Tolomeo M, Grimaudo S, Di Antonietta C, Balzarini J, Hadfield JA, Hamel BA. Eur J Med Chem. 2007; 50: 2273
15. Cushman M, Nagarathnam D, Gopal D, Lin He HM, Hamel CM. Eur J Med Chem. 1992; 35: 2293.
16. Romagnoli R, Baraldi PG, Carrion MD, Cruz-Lopez O, Cara CL, Tolomeo M, Grimaudo S, Cristina AD, Pipitone MR, Balzarini J, Kandil S, Brancale A, Sarkar T, Hamel E. Bio Med Chem. 2008; 18: 5041–5045.
17. Son JK, Zhao LX, Basnet A, Thapa P, Karki R, Na Y, Jahng Y, Jeong TC, Jeong BS, Lee CS, Lee ES. Eur J Med Chem. 2008; 43: 675-682.
18. Amr EA, Mohamed MA, Mohamed SF, Hafez A, Hammam AG. Bio Med Chem. 2006; 14: 5481–5488.
19. Chezal JM, Paeshuyse J, Gaumet V, Canitrot D, Maisonial A, Lartigue C, Gueiffier A, Moreau E, Teulade JC, Chavignon O, Neyts J. Eur J Med Chem. 2010; 45: 2044–2047.
20. Zimbeg GD, Zorc B, Kralj M, Ester K, Pavelic K, Andrei G, Snoeck R, Balzarini J, Clercq

DE, Mintas M. Eur J Med Chem. 2008; 43: 1180-1187.
21. Metobo SE, Jin H, Tsiang M, Kim CU. Bio Med Chem. 2006; 16: 3985–3988.
22. Stevens M, Pannecouque C, Clercq ED, Balzarini J. Bio Pharmacol. 2006; 71: 1122-1135.
23. Zdemir OA, Turan-Zitouni GI, Kaplancıklı ZA, Can GK, Khan S, Demirci S. Eur J Med Chem. 2010; 45: 2080–2084.
24. Siddiqi ZA, Khalid M, Kumar S, Shahid Mk Noor S. Eur J Med Chem. 2010; 45: 264–269.
25. Ali TES. Eur J Med Chem. 2009; 44: 4385–4392.
26. Leal B, Afonso FI, Rodrigues CR, Abreu PA, Garrett R, Pinheiro LCS, Azevedo AR, Borges JC, Vegi PF, Santos CCl Da Silveira FCA, Cabral LM, Frugulhetti ICPP, Bernardino AMR, Santos DO, Castro HC. Bio Med Chem. 2008; 16: 8196–8204.
27. Mishra A, Kaushik NK, Verma AK, Gupta R. Eur J Med Chem. 2008; 43: 2189-2196.
28. Cui Y, Dang Y, Zhang S, Ji R. Eur J Med Chem. 2005; 40: 209–214.
29. Weon Bin Im JWY, Rhee JK, Shim MJ, Kimb WB, Choia EC. Bio Med Chem. 2004; 12: 5909–5915.
30. Hoonur RS, Patil BR, Badiger DS, Vadavi RS, Gudasi KB, Dandawate PR, Ghaisas MM, Padhye SB, Nethaji M. Eur J Med Chem. 2010; 45: 2277–2282.
31. Galya R, Abdrakhmanova F, Carroll I, Damaj MI, Martin BR. Neuropharmacol. 2008; 55: 1287–1292.
32. Menegatti R, Silva GMS, Sudo GZ, Raimundo JM, Sudo RT, Barreiroa EJ, Fragaa CAM. Bio Med Chem. 2006; 14: 632–640.
33. Baraznenok IL, Jonssona E, Claessonb A. Bio Med Chem. 2005; 15: 1637–1640.