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PIPERIDINE SCAFFOLD DRUGS AND THEIR MEDICINAL APPLICATIONS

R. A. Shastri

P. G. Dept. of Chemistry S.B.E.S. College Of Science,
Chhatrapati Sambhajinagar 431001.
Corresponding author E-mail: shastriranjana@yahoo.com

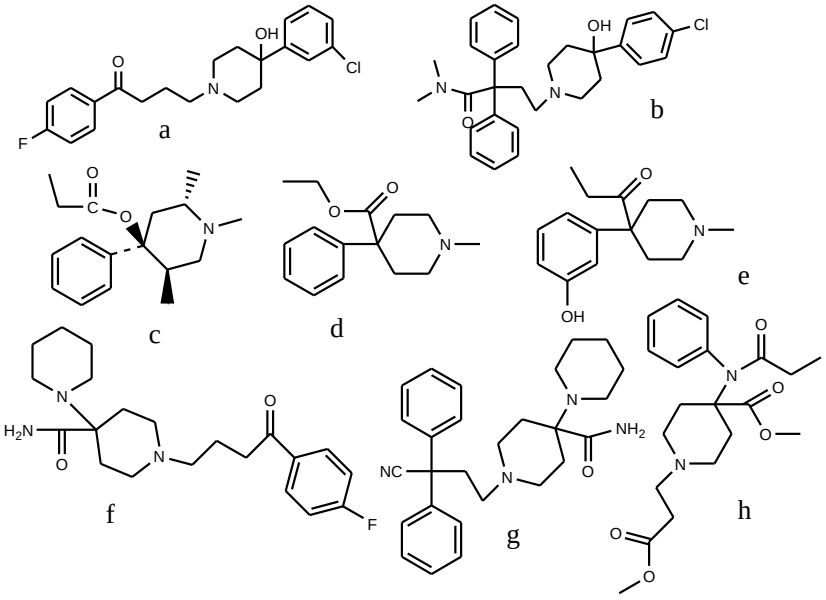
ABSTRACT:
Piperidine containing compounds represents one of the most important synthetic medicinal blocks for drugs synthesis as it has many biological applications such as anticancer, antiviral, antimalarial, antifungal, antihypertensive, analgesics, anti-inflammatory, anti-Alzheimer, antipsychotic and anticoagulant. This review article discusses the various naturally occurring and synthetic piperidine derivatives with applications.

KEY-WORDS:
Piperidine, antimalarial piperidine derivatives, antipsychotic piperidine derivatives.

INTRODUCTION:

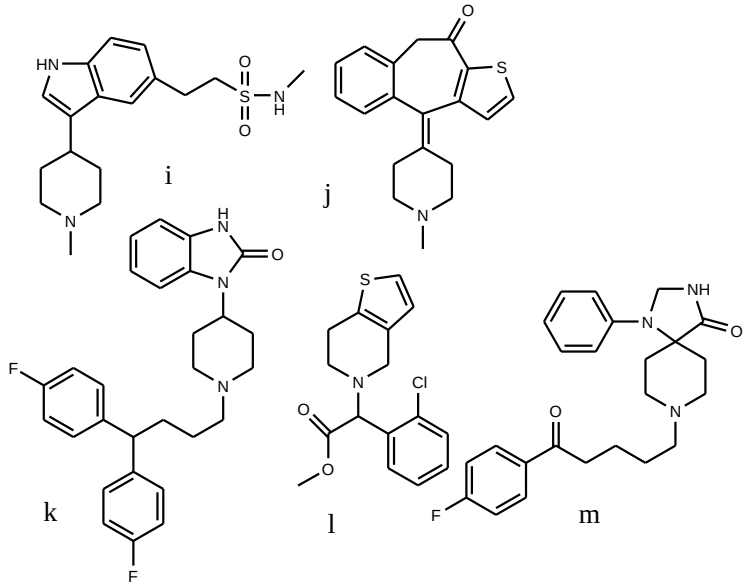
Piperidine is saturated heterocyclic amine found in several pharmaceutical and natural alkaloids with diverse range of medicinal applications such as anticancer, antiviral, antimalarial, antimicrobial, antifungal, antihypertensive, analgesics, anti-inflammatory, anti-Alzheimer, antipsychotic and anticoagulant[i].

Some of the important commercialised Piperidine derivatives used commonly as drugs are Haloperidol,Loperamide,Trimeperidine,Pethidine,Ketobemidone,Pipamperone,Piritramide,Remifentanil,Naratriptan,Ketotifen,Pimazide,Spiperone etc.



Structures of 1,4,4 trisubstituted piperidine based drugs

Haloperidol (a) is used to treat nervous, emotional and mental conditions e.g. schizophrenia. Loperamide(b) is used for recurring or long lasting diarrhoea, ulcerative colitis and short bowl syndrome.Trimeperidine (c) behaves like opioids. Its activity is half to that of morphine. Pethidine (d) is analgesia. It acts by reducing feeling of pain by interrupting the nervous signal between brain and body. Ketobemidone (e) is powerful opioid analgesics. It is useful when pain is not controlled by any other opioid. Pipamerone (f) is used as antipsychotic drug to treat schizophrenia and as a sleep aid for depression.Piritramide (g) used for several pains particularly treatment of colonel cancer also for post operative pains. Remifentanil (h) is opioid analgesia. Naratriptan(i) is used to treat acute headache in adults ketotifen (j) is used to prevent asthma attack. Clopidogrel (l) is an antiplatelet medicine. It prevents platelets from forming dangerous blood clot. Pimozide (k) is used to treat symptoms of tourettes syndrome. Spiperone (m) is a dopamine D_2 receptor antagonist.It is used for studying neurotransmitter receptor.

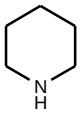


Structures of piperidine and other heterocycle based drugs

This article is written with the aim to provide useful information of piperidine containing drugs which are useful against various diseases.

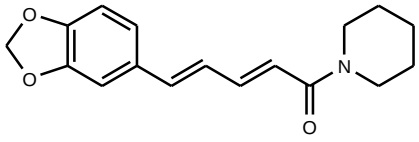
Naturally occurring piperidine used as drug.

Piperidine and piperine are two alkaloids separated from black pepper i.e. from *psilocaulon absimile* and *petrosemonia monarda.*



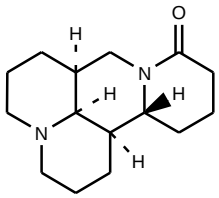
Structure of piperidine Fig.1

Piperidine (fig.1) is heterocyclic moiety with structure $(CH_2)_5NH$ whereas piperine(fig.2) is N-acyl piperidine, it has powerful antioxidant action as it suppresses free radical generation. Its activity is against cancer, inflammation, hypertension, asthma, antidepressant action Piperine also found to have in vivo and in vitro antiproliferative and antimetastatic affects on various types of cancers[ii].



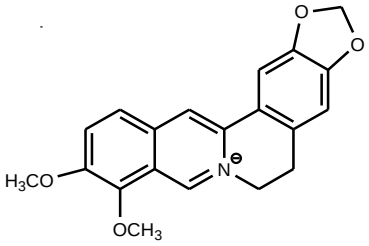
Structure of piperine Fig.2

Matrine is alkaloid extracted from root bark of *saphora flavescens*. It possesses strong antitumor activities in vivo and vitro[iii]. It also possesses immunomodulatory, anti-inflammatory, antibacterial and antioxidant activity.



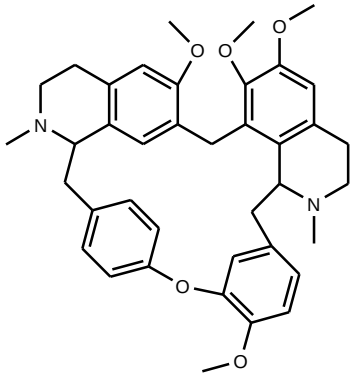
Structure of Matrine. Fig.3

Berberine is bioactive compound that can be extracted from several plants commonly *Berberis.* It lowers blood sugar, increases weight loss and improves heart health, also used to treat liver diseases, liver cancers[iii.]



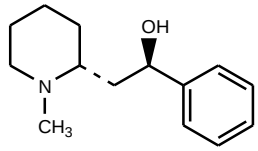
Structure of Berberine. Fig.4

Tetrandrine is bisbenzylisoqninoline alkaloid extracted from Chinese herb *Radix-Stephania tetrandrae*. It is a calcium channel blocker, vasodilator used to treat hypertension. It has anti-inflammatory, immunologic and antiallergic effects. It is also used to treat liver diseases, liver cancers[iii].



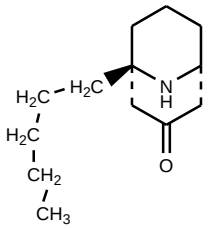
Structure of Tetrandrine. Fig.5

Sedamine was isolated from *sedum acre* which inhibits pea diamine oxidase. It acts on brain to produce a calming effect[iii].



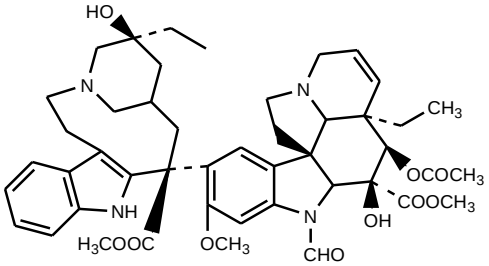
Structure of Sedamine. Fig.6

Adaline is a defensive alkaloid isolated from *Adalia bipunctata*.



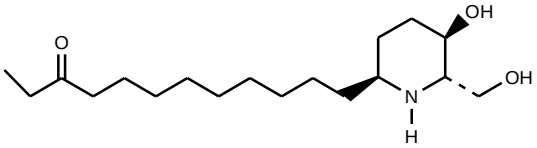
Structure of Adaline. Fig.7

Vinblastine is extracted from *Vinca Rosea*. It is an antineoplastic agent. It is used to treat all types of cancers such as Hodgkin's lymphoma, lung cancer, bladder cancer, melanoma and testicular cancer[iv].



Structure of vinblastine. Fig.8

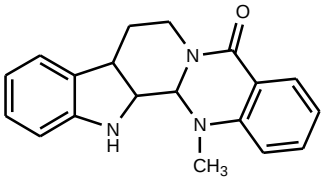
Presopinine was isolated from the leaves, stems and roots of *Prosopis Africana* and has a wide variety of biological activities such as sedatives, hypotensive, spasmolytic and antiseptics[iii].



Structure of Prosopinine. Fig.9

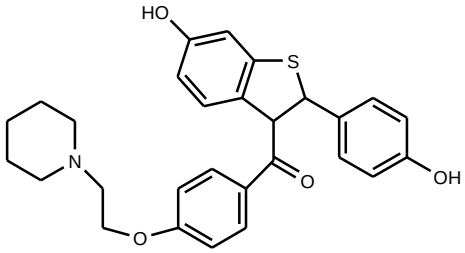
Evodiamine is an alkaloid extracted from the plant genus Tetradium. It inhibits human breast cancer NCI/ADR Res cells [v, vi,vii]. It is used for the treatment of amenorrhea, postpartum

haemorrhage, headache and gastrointestinal disorders. It is also used for reducing pain, swelling, B.P. and stimulates heart.



Structure of Evodiamine. Fig 10

Raloxifene (fig11) is used for reducing risk of invasive breast carcinoma in postmenopausal women by acting as oestrogen blocker[viii].

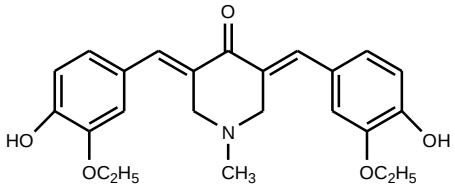


Structure of Raloxifene. Fig.11

SYNTHESIZED PIPERIDENE DERIVATIVES

Anticancer Activity in Piperidine Derivatives

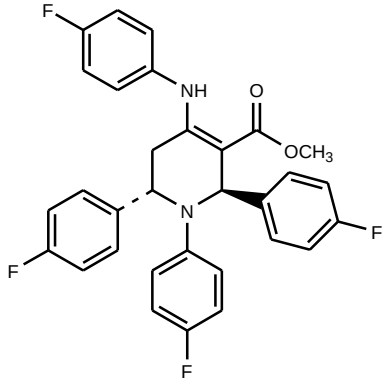
Khairia and co-workers synthesized two piperidine analogous among which compound (fig12) found to be effective in decreasing cancer cells[ix].



(1)

Structure of N-methyl-4 piperidone derivatives. Fig.12

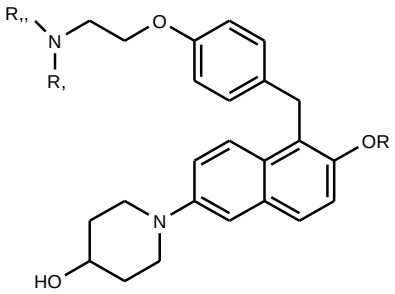
Suvankar and co-workers studied twenty five piperidine derivatives and found to be free radical scavengers. Among these compound (fig.13) was found to be potent antitumor agent[x].



(2)

Structure of piperidine derivatives. Fig.13

Amitabh and co-workers synthesized piperidine derivatives and evaluated for breast cancer cells and found to have potent cytotoxic activity (3a&3b). These compounds had greater activity than Tamoxifen and Raloxifene[xi].

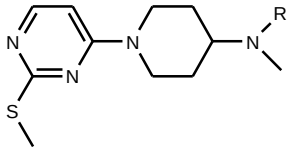


	R-R
3a	$(CH_3)_2$-CH($CH_3)_2$- $CH_3)_2$
3b	-$(CH_2)_6$

(3)

Structure of hydroxypiperidine derivatives. Fig.14

Yangun and co-workers synthesized piperidine derivatives among these 4a&4e (fig.15) showed remarkable inhibitory effect on human breast cancer cells[xii].

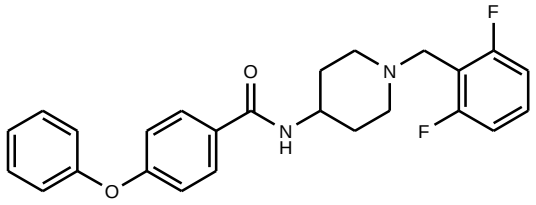


(4)

	R
4a	p-cyanobenzyl
4b	2-chloro-6-fluro benzyl
4C	2,4dichlorobenzyl
4d	2,6dichlorobenzyl
4e	2, chlorobenzyl

Structure of N-methyl piperidine derivatives. Fig.15

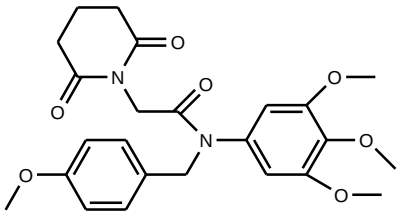
Jin and co-workers synthesized N-(piperidine-4-yl) benzamide compounds, these compounds found to be effective against cancer cells. SAR study showed that the presence of carboxyl, nitro, halogen, methyl group on benzene ring increases the cytotoxic activity. Among these compound 5 (fig.16) was found to have maximum cytotoxic activity[xiii].



(5)

Structure of N-(piperidine-4-yl) benzamide derivatives. Fig.16

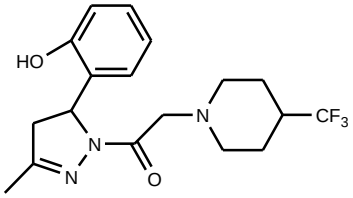
Dong and co-workers synthesized a new series of piperidine derivatives and found to be anticancer active. Among these, compound 6 (fig 17) was found to have strong proliferative activity[xiv].



(6)

Structure of dioxopiperidin-1-yl derivatives. Fig.17

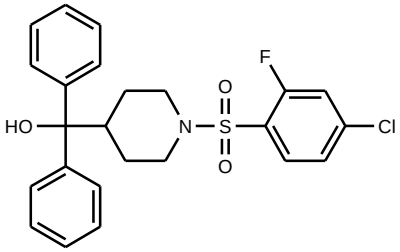
Xin and co-workers prepared 5-phenyl N-piperidine ethenone 4-5 dihydropyrazoles and evaluated for anticancer activity. Among these compound 7 (fig18) shows pronounced activity against cancer cells. When CF_3 was replaced by nitro or amide functional group decreases anticancer activity[xv].



(7)

Structure of trifluoro methyl piperidine. Fig.18

Benaka and co-workers synthesized new diphenyl (piperidine-4-yl) methanol derivatives and evaluated for antiproliferative activities, compound 8(fig.19) showed cytotoxic activity. If carbon chain length is increased it reduces the antitumour activity and presence of electron donating group such as Cl, F increases the antitumour effect[xvi].

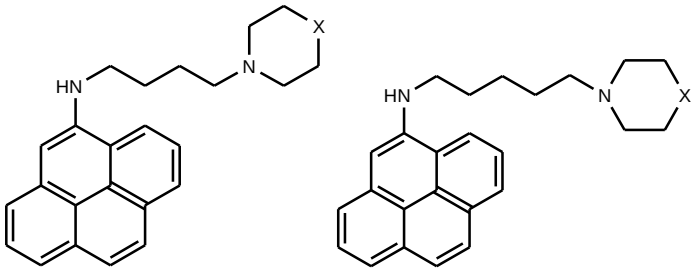


(8)

	x
10a	Cl
10b	Br

Structure of diphenyl (piperidine-4-yl) methanol derivatives. Fig.19

Debashish and co-workers synthesized eight pyrenyl derivatives and evaluated for antiproliferative action. Compound 9a & 9b were the most potent cytotoxic agents. Antiproliferative action was found to have for four carbon linkers than five carbon linkers[xvii].

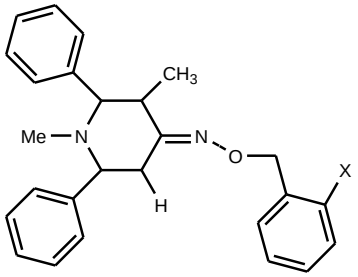


a (9) b

Structure of pyrenyl piperidine derivatives. Fig 20

Antimicrobial activity in piperidine derivatives

Chennan and co-workers prepared piperidine-4-one oxime derivatives and evaluated for their in vitro antimicrobial activity compound 10a&10b (fig21) showed strong antifungal activity against *Aspergillums flavus and candida-51*[xviii].

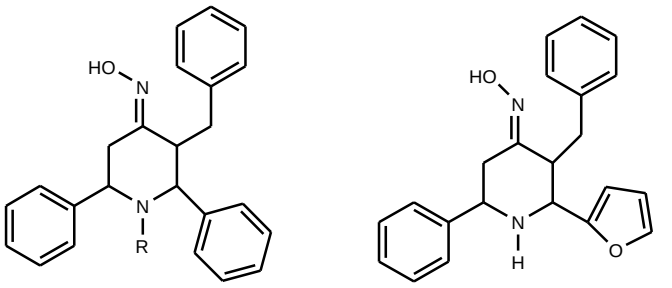


(10)

Structure of piperidine-4-one oxime derivatives. Fig21

Jayaraman and co-workers synthesized a series of piperidone derivatives, compounds were evaluated for antimicrobial effect against various types of bacteria and fungi. Compound 11a and 11b (fig22) showed good antibacterial activity against *Bacilius subtilis, E.coli, K.pneumariae and s.faecalis.*

Compound 11b and 12 (fig.22) showed antifungal activity against *A. niger, A. flavus, C. neoformans, Candid 6 & Candida 51*[xiv].



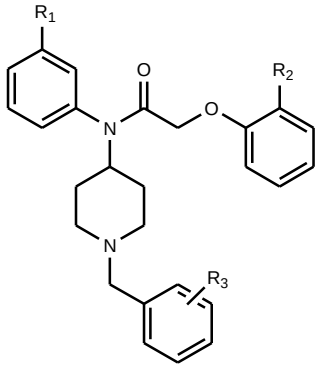
	R
11a	H
11b	COH

11 12

Structure of phenyl piperidine-4-one oxime derivatives. Fig 22

Antimalarial activity in piperidine derivatives

Rokhyatou and co-workers synthesized 1,4 disubstituted piperidine derivatives and evaluated for chloroquine sensitive and chloroquine resistant strains of *P. falciparum*. It was found compounds 13a-c (fig.23) as most potent drugs[xx].



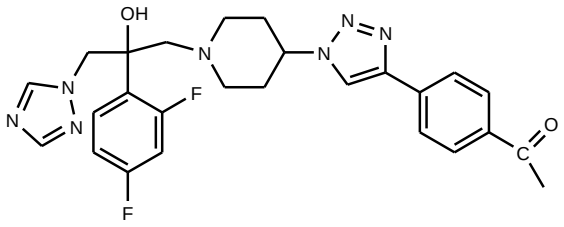
	R_1	R_2	R_3
13a	H	H	H
13b	F	Cl	H
13C	F	Cl	Br

(13)

Structure of 1, 4 disubstituted piperidine derivatives. Fig23

Antifungal activity in piperidine derivatives

Zhigan and co-workers synthesized piperidinyl triazole derivatives as antifungal agents. Among these, compounds 14 and 15 has pronounced antifungal activity[xxi].



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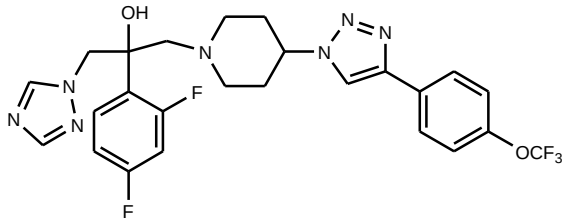

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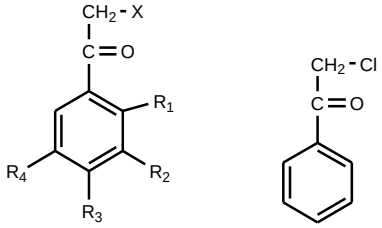
Structure of piperidinyl triazole derivatives. Fig 24

Antihypertensive activity is piperidine derivatives.

Shamim and co-workers synthesized N-substituted phenacyl piperidine derivatives and evaluated for hypotensive activity, compounds 16, 17a & 17b exhibited mild antihypertensive activity[xxii].

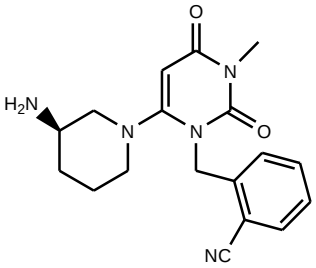


(17) (16)

	R_1	R_2	R_3	R_4	X
17a	H	OH	OH	H	Cl
17b	H	NO2	H	H	Br

Structure of N-substituted phenacyl piperidine derivatives. Fig 25

Alogliptin is piperidine containing drug used to treat high blood sugar levels caused by type 2-diabetes. It works by increasing substance in the body that makes the pancreases release more insulin.

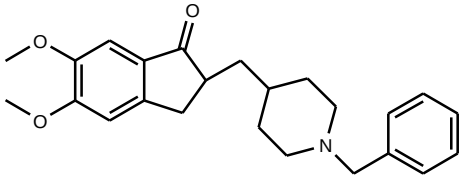


(18)

Structure of Alogliptin Fig 26

Alzheimers activity in piperidine derivatives.

Gunhild studied the effect of Donepezil. Donepezil is piperidine containing drug used in neuropsychiatric disorders in patients with Alzheimer's disease[xxiii].



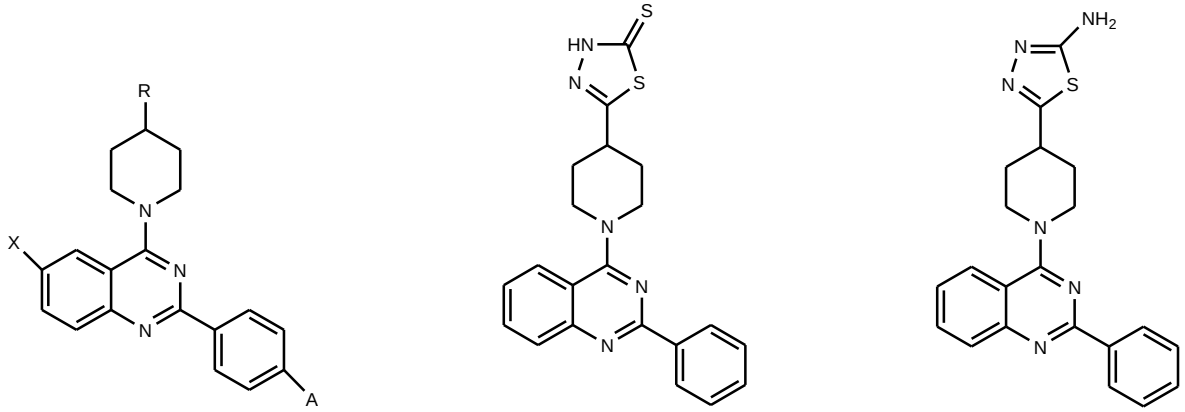
(19)

Structure of Donepezil Fig 27

Analgesics and Anti inflammatory activity in piperidine derivatives

Ahmed and co-workers synthesized 2,4,6 trisubstituted quinazoline derivatives having piperidine nucleus and evaluated for analgesics to have higher analgesic effect than reference standard drug indomethacin. Compound 20a, 20b, 20c, 20e, 21 and 22 (fig28) got both analgesics and anti-inflammatory effect[xxiv].

	X	A	R
20a	H	H	Me
20b	H	H	Ph
20c	I	H	Ph
20d	Br	Cl	Me
20e	H	H	CO2 Et

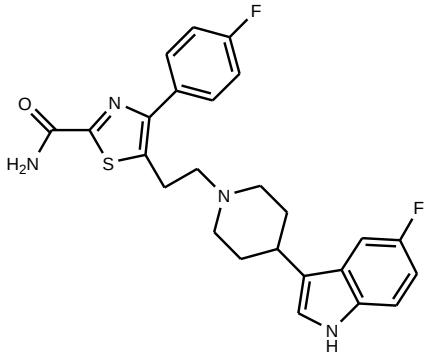


(20) (21) (22)

Structure of 2,4,6 trisubstituted quinazoline derivatives. Fig 28

Antipsychotic activity in piperidine derivatives

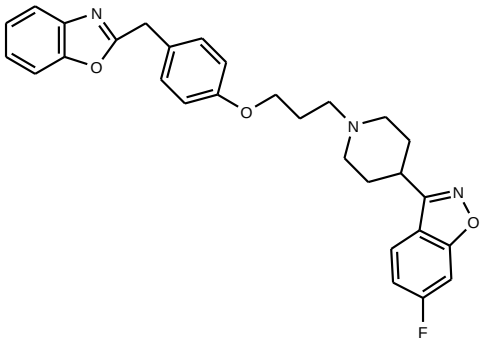
Takeo and co-workers synthesized piperidinyl 6-fluoro indole derivatives and found to have affinity to dopamine receptor and showed to have antipsychotic effect[xxv].



(23)

Structure of piperidinyl 6-fluoro indole derivatives. Fig 30

Ling and co-workers synthesized new benzoxazole piperidine derivatives. All these derivatives have affinity to dopamine receptors. Among these following compound 24 (fig 31) was found to have best antipsychotic effect[xxvi].

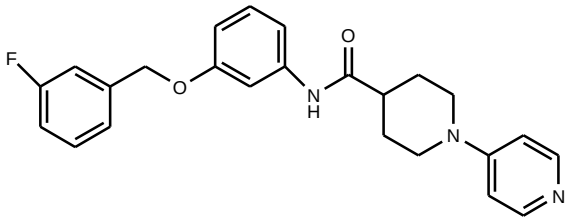


(24)

Structure of benzoxazole piperidine derivatives. Fig 31

Anticoagulant activity in piperidine derivatives

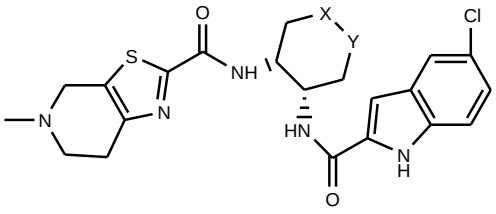
Modesto and co-workers synthesized 4-(piperidin-1-yl) pyridine derivatives. Among these compound 25(fig 32) showed good anticoagulant property[xxvii].



(25)

Structure of 4-(piperidine-1-yl) pyridine derivatives. Fig 32

Akiyoshi and co-workers synthesized two racemic piperidine derivatives. Among the prepared compounds 26a-e (fig 33) possesses more anticoagulant activity[xxviii].

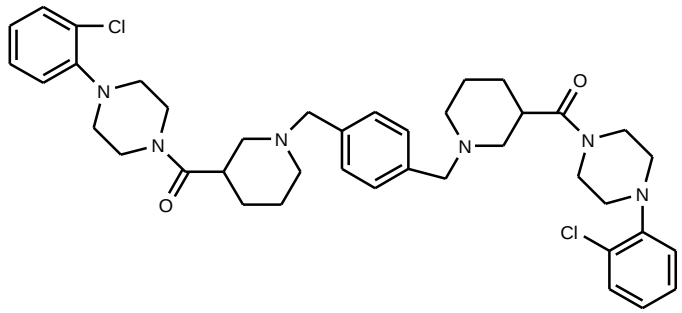


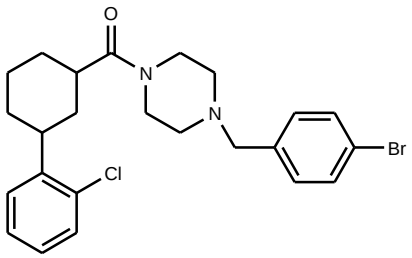
	x	y
26a	NCO_2tBu	CH_2
26b	NH	CH_2
26C	$NCOCH_3$	CH_2
26d	NSO_2CH	CH_2
26e	NCO_2Et	CH_2

(26)

Structure of piperidine diamine derivatives. Fig 33

Khairia and co-workers synthesized a series of carbamoyl pyridine and carbamoyl piperidine derivatives. These compounds possesses platelet aggregation inhibition effect. Among these compound 27 and 28 (fig34) possesses most potent antiplatelet aggregation effect[xxix].





(27) (28)

Structure of Carbamoyl piperidine derivatives. Fig 34

CONCLUSION:

This review explains the importance of piperidine nucleus along with other heterocyclic nuclei in controlling various diseases.

Naturally occurring piperidines display various effects against cancer, inflammation, hypertension, asthma, antidepressant and antioxidants. By considering the importance of derivatives various synthetic piperidine derivatives were presented having different pharmacological effects such as antihypertensive, analgesics, anti-Alzheimer, analgesics, anti-inflammatory, antipsychotic and anticoagulant activity.

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