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A Brief Insight into Isoxazole Analogues

Chiranjit Jana[1] and Subhasis Banerjee*[2]

[1]*Department of Pharmaceutical Technology, Gupta College of Technological Sciences, Ashram More, G.T Road, Asansol-713301. Bardhamann, West Bengal, India*
[2]*Department of Pharmaceutical Chemistry, Gupta College of Technological Sciences, Ashram More, G.T Road, Asansol-713301. Bardhamann, West Bengal, India*

ABSTRACT

The isoxazole ring is a universal centroid of many synthetic compounds with various therapeutic efficacies. The ongoing review deals with some of the advancement during the last few decades in medicinal chemistry research of isoxazole derivatives as anticonvulsant, antibacterial, antidepressants, antitumor, antithrombin, antirhinovirus etc. The structure activity relationships (SARs) study of many isoxazole analogues have been discussed in such a manner, that it will definitely attract budding researchers to start up a novel medicinal chemistry project considering this sought after scaffold.

Keywords: Isoxazole, structure activity relationships (SARs), antitumor, antithrombin

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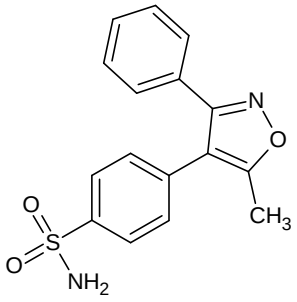
INTRODUCTION

The Isoxazole ring system belongs to a much studied class of compound. In the last few decades, the chemistry of isoxazoles and their fused heterocyclic derivatives have received considerable attention owing to their significant and effective biological activity. Isoxazole moiety has been incorporated into a wide variety of therapeutically interesting drug candidates including AMPA receptor agonist, antithrombin activity, anti-rhinovirus agents, antidepressants, antinociceptive activity, antibacterial, anticonvulsant activity, nonnucleoside HIV-1 reverse transcriptase inhibitor, antitumor, cox-1/cox-2 inhibitor, HDAC inhibitor, antitubulin activity, 5-HT reuptake inhibitor, adrenoceptor antagonist, humoral immune response inhibitor and the neurological disorders such as schizophrenia. An attempt is being further made to explore it in an illustrated manner owing to their clinical significance in medicinal chemistry research.

Some of commercially available drugs with isoxazole nucleus are as follows:
antiarthritic as Valedecoxib (1), anticonvulsant as Zonisamide (2), antirheumatoid as Leflunomide (3), antibacterial as Acetylsulfisoxazole (4), Drazoxol (5), Cycloserine (6), sulfamethoxazole (7), Oxacillin (8), anticancer as Acivicin (9), antidepressant as Isocarboxazid (10) and Gaboxadol (11).



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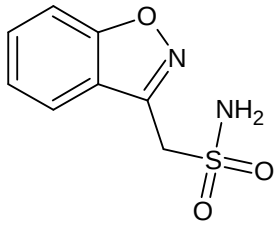

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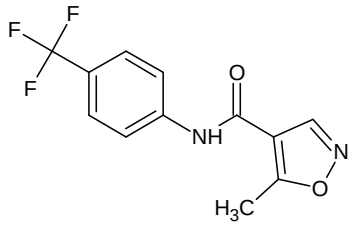

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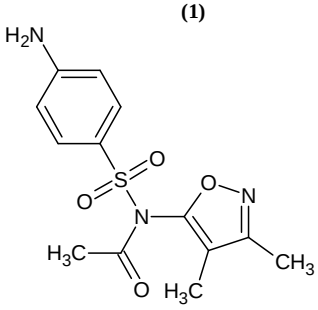

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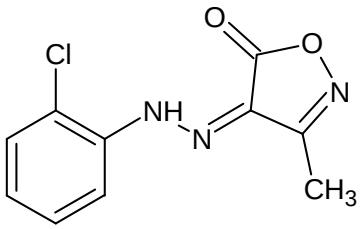

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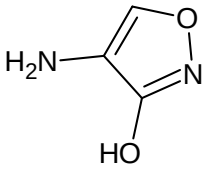

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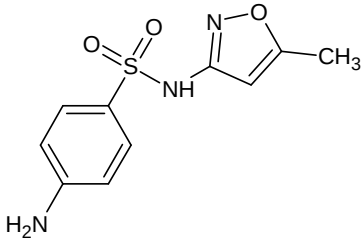

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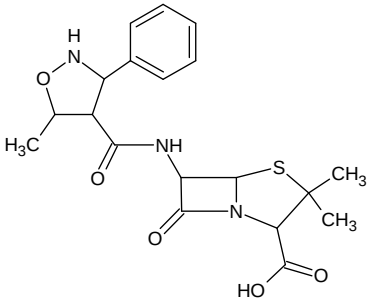

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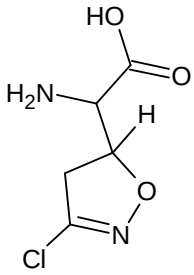

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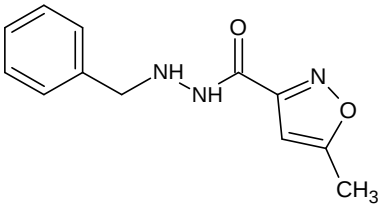

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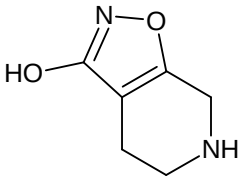
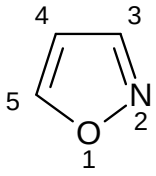


(11)

In addition to these important biological applications, isoxazole are also of great utility in preparative organic chemistry, viz, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds, e.g.-isoxazole[5,4-b]pyridine, quinoline, isoquinoline, pyridazine, pyrimidine and pyrazine ring.

CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIPS

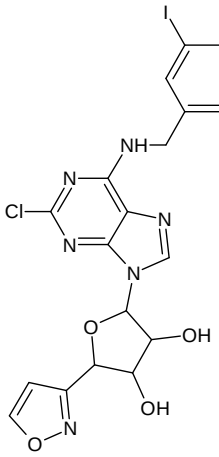
Isoxazoles (12) and their derivatives have been recognized as highly useful in medicinal chemistry research. Isoxazole is an azole with an oxygen atom next to the nitrogen. Isoxazolyl is the univalent radical derived from isoxazole with molecular formula C_3H_3NO.



(12)

Monosubstituted isoxazoles

Mogensen *et al* [1] reported the synthesis of compounds (13) and (14) and evaluated their binding affinity towards human A_3 receptors, with relatively weak binding affinity observed to A_3 and AZ_{2A} receptors. Many selective A_3 receptor agonists e.g. N-(3-iodobenzyl)adenosine- 5´-methyluronamide (IB-MECA) contain a 4´-ribosyl alkylamide moiety.



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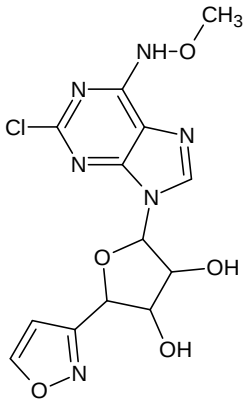
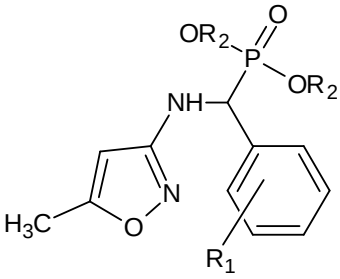


(14)

It was observed that this amide and other 4´-functional group could be replaced with an isosteric isoxazole and the target molecules retained potent binding to the recombinant human A_3 receptor.

A series of α-aminophosphonates containing isoxazole (15) was reported by Song *et al* [2]. The newly formed compounds were found to possess moderate antitumor activities against PC3 and A431 cells.



R_1=2-F, 4-F

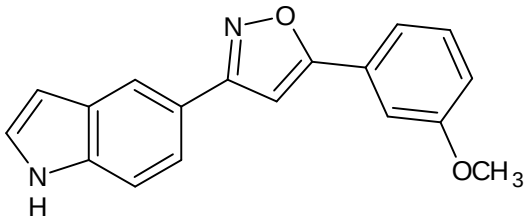
R_2=CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$,C_4H_9

(15)

Disubstituted isoxazoles

3, 5-disubstituted isoxazoles

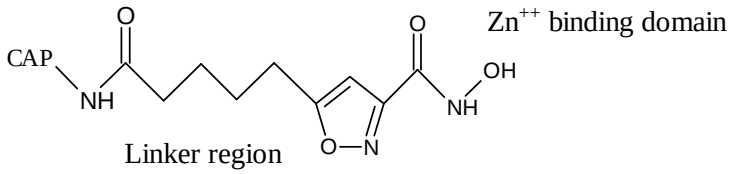
A series of 3-(indol-2-yl)-5-Phenylisoxazoles was studied by Tohid *et al* [3] for their *in vitro* growth inhibitory activity of against the Colo320 (colon) and Calu-3 (lung) human cancer cell lines. The Compound (16) with IC_{50} values, 10 mM and 20 mM respectively was found to be the most active in the entire series.



(16)

Further studies on human bronchial smooth muscle cells (BSMC) indicated that the above compound (16) had little or no effect on cell viability in this normal cell line control, suggestive of selective pro-apoptotic antitumour effects. A series of hydroxamic acid based histone deacetylase inhibitors (HDAC) containing an isoxazole moiety adjacent to the Zn-chelating hydroxamic acid, was reported by Tapadar *et al* [4]. Compound (17) showed nanomolar activity in the HDAC isoform inhibitory assay and exhibited micro molar inhibitory activity against five pancreatic cancer cell lines. The design was made considering the prototypical structure of Suberoylanilide Hydroxamic Acid (18), the lead compound in the development of HDAC inhibitor. Insertion of an isoxazole moiety at the linker region, keeping the rest pharmacophoric groups as such did not give rise to an even comparable inhibition as that of the commonly available hydroxamic acid derivative.

CAP: different aromatic heteroaromatic and alicyclic groups



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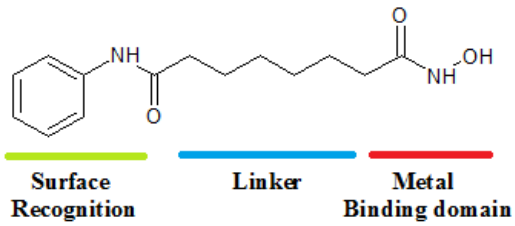
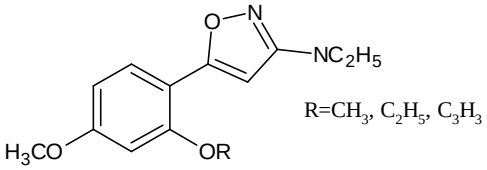


(18)

Mazzei *et al* [5] reported the synthesis of a new series of substituted 5-phenylisoxazoles (19) and evaluated them against representatives of the entero and rhinoviruses and explored their antiviral spectrum in assays against other DNA and RNA viruses, HIV- 1. Compound (20) showed the highest clinical efficacy.



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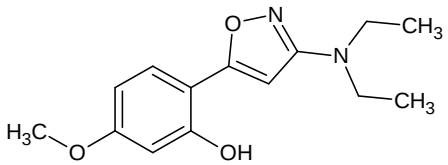
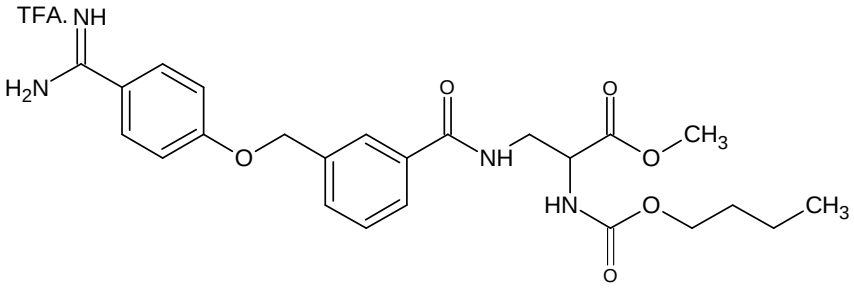


(20)

Xue *et al* [6] inferred that the replacement of benzamide core of the most active compound XU057 (21) with an isoxazolecarboxamide fragment resulted in a significant improvement in *in vivo* activity. The isoxazolecarboxamide analogue XU065 (22) showed a dose dependent antiplatelet effect following oral administration to dogs.



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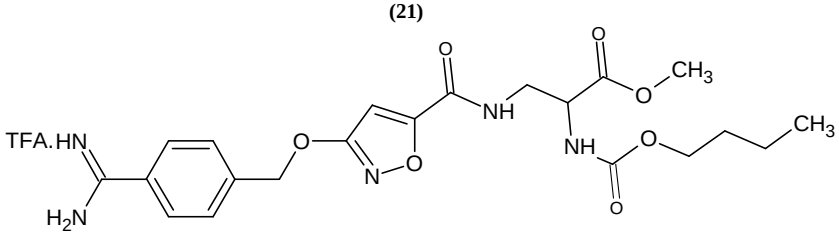
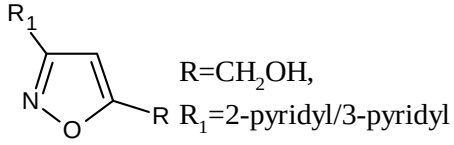


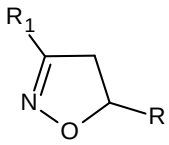
(22)

A series of 3,5-disubstituted isoxazoles (23) and isoxazolines (24) was synthesized by Vrzheshch *et al* [7] to check their antiplatelet aggregation inhibitory potential. Most of the compounds in the same series lacked proaggregatory activity up to 1 mM, but inhibited, within the range from 1 to 1000 µM, both arachidonate-induced platelet aggregation and the second phase of ADP-induced platelet aggregation (primary ADP-induced aggregation was not affected).



R=CH_2OH,
R_1=2-pyridyl/3-pyridyl

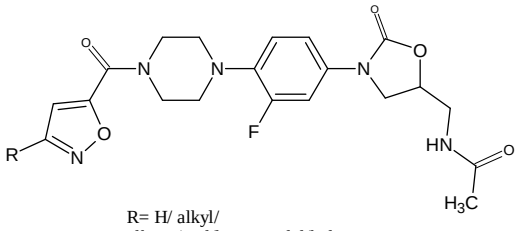
(23)



R=$COOC_2H_5$
R_1=3-pyridyl/4-pyridyl

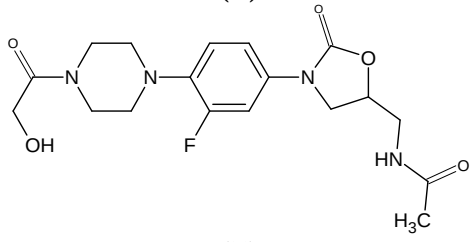
(24)

Pae *et al* [8] reported that an isoxazolyl substituent being present in the series of compounds (25) could enhance largely the activity of cephalosporins especially against Gram-positive bacteria, Based on the findings, a positive effect of an isoxazole group on the activity of oxazolidinone, Eperezolid (26) was anticipated. The isoxazole group was introduced to the nitrogen of piperazine via a methylene or a carbonyl linkage.



R= H/ alkyl/
alkoxy/aryl/heterocyclyl/halogen

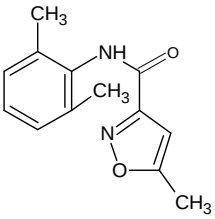
(25)



(26)

Eddington *et al* [9] synthesized an isomeric 5-methyl-substituted isoxazoles (27) with the 3-methylsubstituted (28) isoxazoles and evaluated their anticonvulsant activity. Their work provides potent, orally active class of compounds with a hitherto distinct mechanism of anticonvulsant activity.

To investigate the importance of the pattern of substitution in the heterocyclic ring for the antitubulin and the antiproliferative activities, Kaffy *et al* [10] developed a new series of CA4 analogues (29) to (33). The synthesis and biological activities of a series of CA4 analogues with a five membered heterocycle as linker of the two aromatic rings of CA4: isoxazole and other heterocyclic moieties with adjoined nitrogen and oxygen are of clinically significant.



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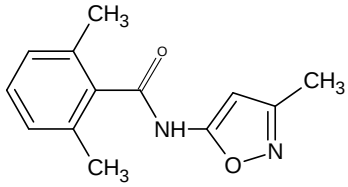

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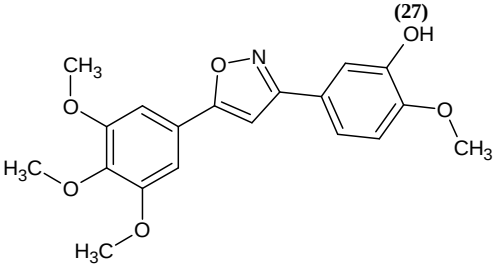

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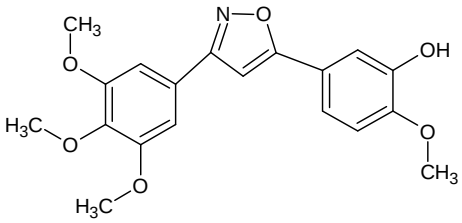

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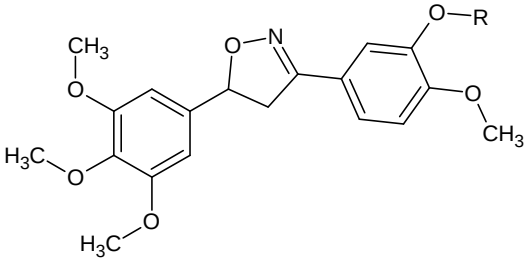
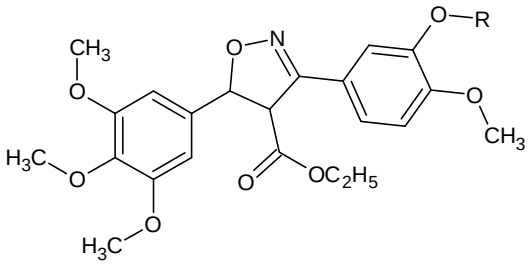
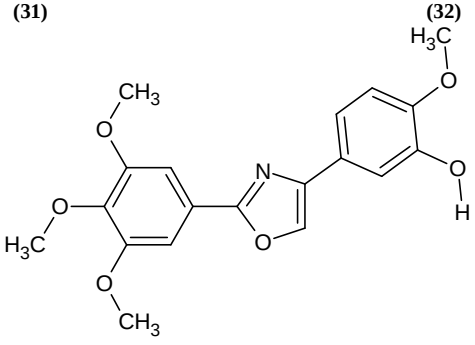




R=tert-butyldimethylsilane

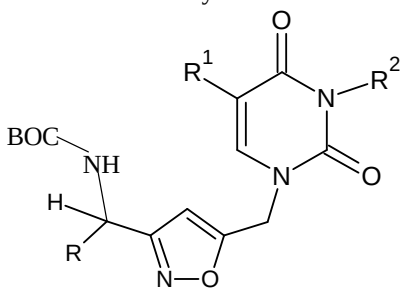
(31) **(32)**



(33)

Whereas, the other derivatives, with a methine (29, 30), a methylene (31), an exocyclic carboxylate or amido group (32) or a nitrogen atom (33) at 4th position were ineffective in the tubulin assay (IC_{50} values > 25 µM).

The antiviral activities was reported to be low when Lee *et al* [11] started synthesizing 5´-hydroxylated isoxazole and isoxazoline nucleosides and evaluated them against various viral strains. Upon refining the native structure (34) they found a dramatic shift in efficacy.



R= CH_3, $CH_2C_6H_5$, $CH(CH_3)_2$

R^1= CH_3, F

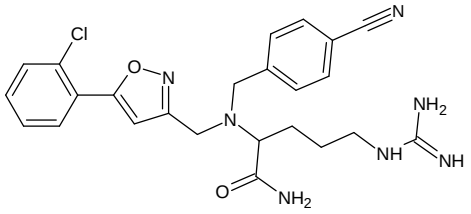
R^2= benzyl

(34)

The following considerations they made in the ligand optimization process:
i. use of rigid isoxazole heterocycles as surrogates for conformationally restricted deoxyriboses ii. introduction of the additional methylene unit between isoxazole and nucleobase to render conformational flexibility

iii. easy incorporation of chiral amino functionality by using α-amino acids as chiral starting materials.

In an effort to develop anti haemorrhagic agent, Batra *et al* [12] reported a series of 3-substituted-phenyl-5-isoxazole carboxaldehydes, out of which, compounds (35) – (37) exhibited more than 50% protection in the bleeding time at the same dosage of 30 mM.



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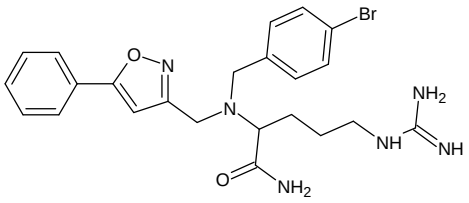

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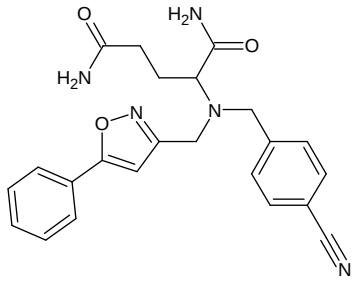
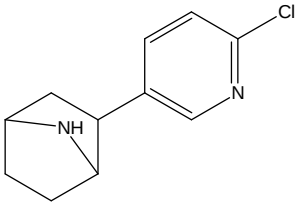


(37)

Considering the deleterious effect of epibatidine (38), an alkaloid with specific agonism at neuronal acetylcholine receptor (nAChR), Avenoza *et al* [13] developed two conformationally restricted ABT418 analogues (39). Replacement of pyridyl moiety in both, compound (38) and nicotine with a methylisoxazole resulted in a small positive shift in activity. Synthesized compounds showed significant nAChR agonism property with an additional benefit against pain.



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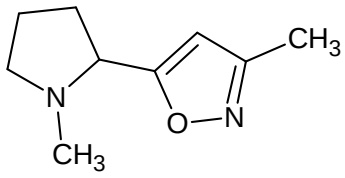
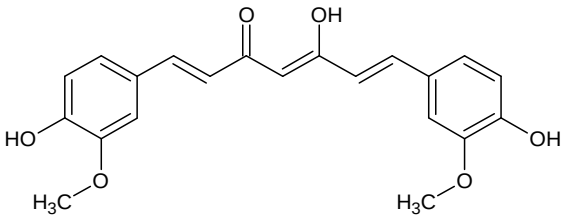


(39)

Anti nociceptive property was best observed for the compounds in their protonated form.

Curcumin (40) are naturally occurring antioxidants with a plethora of other clinical benefits. Selvam *et al* [14] proposed the synthesis and biological evaluation of few isoxazole linked curcumin derivatives. It was found to be quite interesting that compounds (41) and (42) have demonstrated highest anti-inflammatory activity owing to its affinity towards COX-2. They do possess significant free radical scavenging activity as well.



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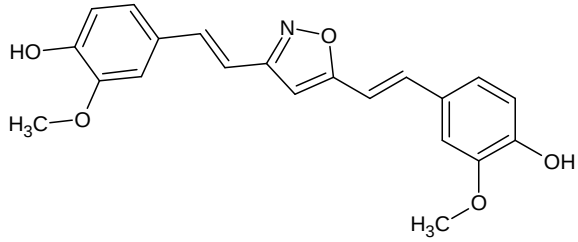

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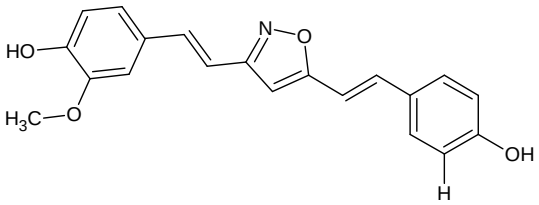
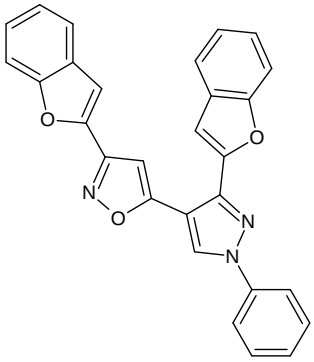


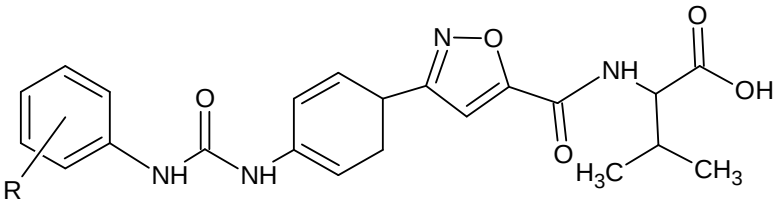
(42)

The synthesis and a rare molluscicidal effect of a series of isoxazole analogue was reported by Shehry *et al* [15]. Except compound (43), all other showed very weak activity below 5 ppm compared to the standard molluscicidal agent.



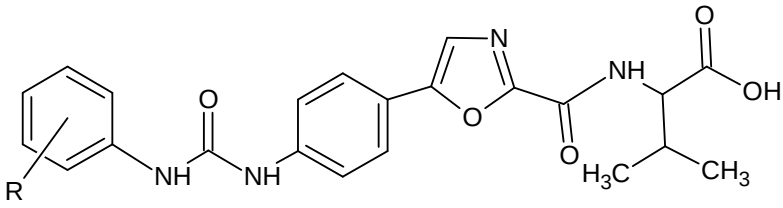
(43)

A series of 3-phenylisoxazoles (44) and 5-phenyloxazoles (45) were synthesized and evaluated their inhibitory influence over hDGAT1 by Jadhav *et al* [16].



R=2-Cl, 3-Cl, 4-Cl, 3-Trifluoromethyl, 3,4-Dimethyl, 2-Phenoxy-4-Chloro

(44)

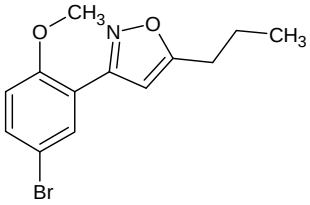


R=2-Cl, 3-Cl, 4-Cl, 3-Trifluoromethyl, 3,4-Dimethyl, 2-Phenoxy-4-Chloro

(45)

The isoxazoles have shown superior inhibitory activity over oxazoles.

Considering the clinical significance of anti-inflammatory drugs, Lee *et al* [17] focused their study in modifying the soft spots (e.g., phenol, olefin) as observed in many anti-inflammatory drugs and composing the polar surface area with heterocycles as isoxazole and triazole. The compounds with the stated modification are (46)-(50).



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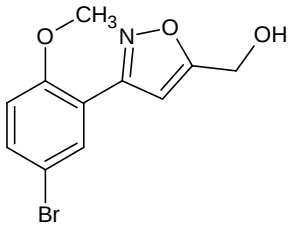

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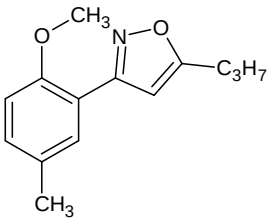

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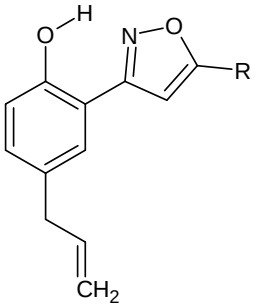

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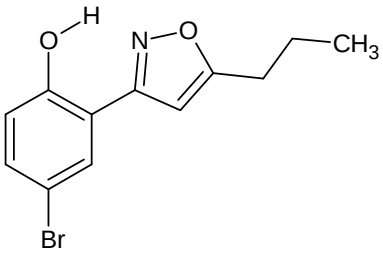
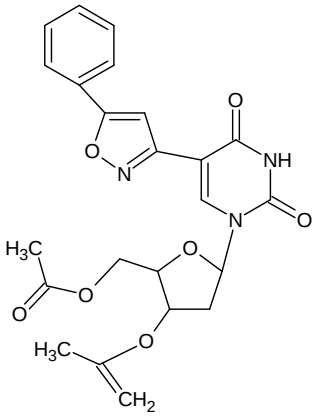


(50)

Most of the compounds under study exhibited inhibitory effects on COX-2 and PGF_1 production but not macrophage NO production.

The synthesis of C5-(isoxazol-3-yl)-pyrimidine nucleosides through 1,3-dipolar cycloaddition was documented by Guo *et al* [18]. All the compounds were further tested for their antileishmanial property.



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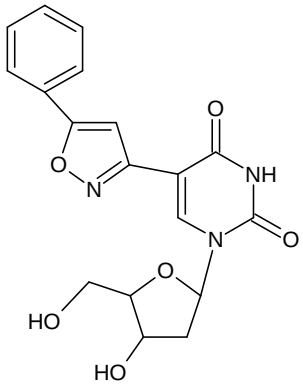
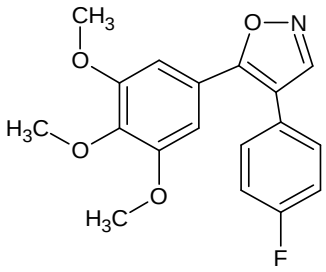


(52)

In vitro antileishmanial activity was observed in most of the C5-(isoxazol-3-yl)-pyrimidine nucleosides.

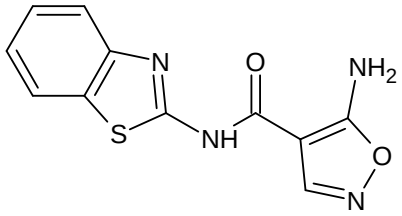
4, 5-disubstituted isoxazoles

In order to evaluate the antiinvasive property of 3,5-Disubstituted isoxazole Roman *et al* [19] came up with a disappointing note, which further led them to develop yet another disubstituted (position altered) isoxazoles. Compound (53) however, proved its potency up to 1 µmol L^{-1}, and thereby distinguished itself clearly from the rest of the set.



(53)

Another structural modification was observed when Bondock *et al* [20] tried to link benzothiazole nucleus to the 4th position of isoxazole by means of amide group in compound (54). Weak to moderate antimicrobial (Gram +ve) activity with MIC values (25–100 mg/mL) clearly indicates for further optimization of the above bonding skeleton.

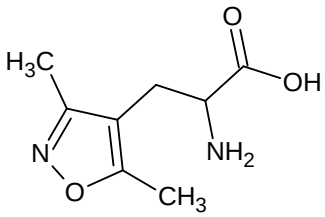


(54)

Trisubstitutedisoxazoles

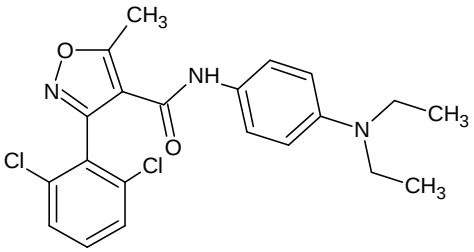
3, 4, 5-trisubstituted isoxazoles

Considering the clinical importance of neuroexcitant amino acids, Pajouhesh *et al* [21] developed a facile way to synthesize isoxazole containing amino acids, 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid (AMPA) (55).

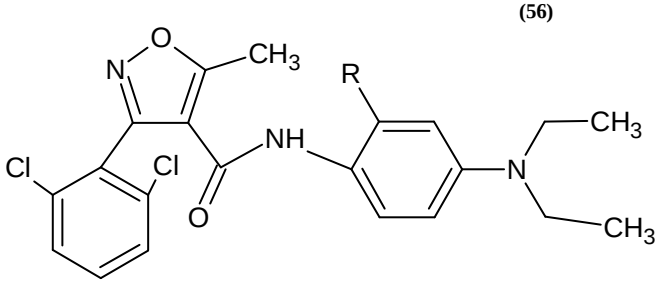


(55)

In search of a novel potent ghrelin receptor antagonists, Xin *et al* [22] reported the synthesis of a series of isoxazolecarboxamide derivatives. Preliminary structure–activity relationship (SAR) revealed that the replacement of the isoxazole core was not successful, while extension at the position 5 of isoxazole ring led to the development of analogs with >10-fold improvement in potency. Compounds (56), with an electron withdrawing group at ortho position enhances receptor affinity and functional activity, whereas substitution at other positions, meta or para was of lesser importance. It was also observed that substituent at ortho position of anilino phenyl (57) seemed to be beneficial to improve binding affinity and functional activity.



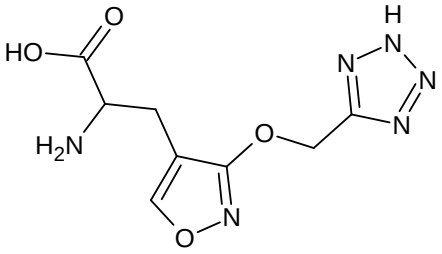
(56)



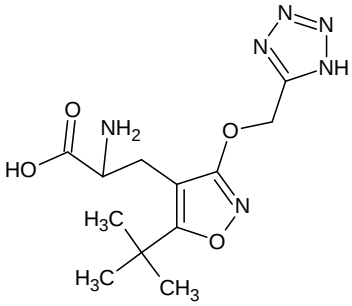
R=CN, CF_3, CH_3, C_2H_5, OCH_3

(57)

Frolund *et al* [23] reported the synthesis of two tetrazolyl isoxazole analogues (58) and (59) of (RS)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), a selective AMPA receptor agonist, and (RS)-2-amino-3-(5-tert-butyl-3-hydroxy-4-isoxazolyl)propionic acid (ATPA), a GluR5-preferring agonist. Compounds (58) and (59) showed micromolar affinities in the AMPA, KA and NMDA receptors.

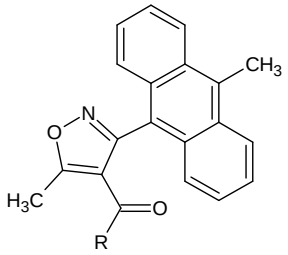


(58)



(59)

Dimeric analogs of anthracenylisoxazole amides (AIMs) were prepared, evaluated and found to have highest efficacy to date for this class of anti-tumor compounds against the human glioma Central Nervous System cell line SNB-19. Gajewski *et al* [24] reported the anticancer activity of a new series of anthracenylIsoxazole amides (60), this novel class of compounds exert their effect by stabilization of quadruplex (G4) DNA, either at the telomere4 and/or specific oncogenes.

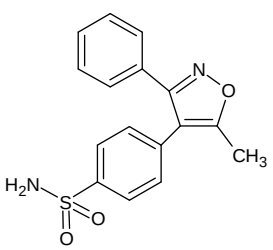


R= $-OC_2H_5$, -OH, -Cl

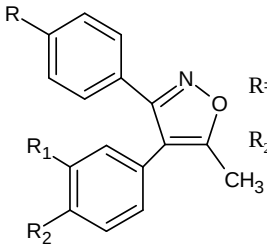
(60)

Owing to their incease gastric tolerance and potency selective COX II inhibitors have occupied a considerable market in pain therapy. In the process of developing an improved route of synthesis for valdecoxib (61) and its synthetic analogues (62) and (63), Dadiboyena *et al* [25] considered the most prevalent 3,4-Diarylisoxazole scaffold

and subsequently found as NSAIDs, protein kinase inhibitors, hypertensive agents, and estrogen receptor (ER) modulators.



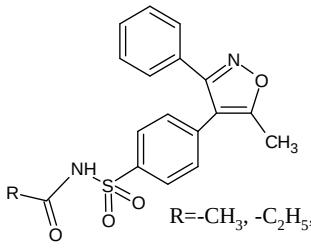
(61)



R=R_1=H, F;

R_2=H, F, SO_2NH_2

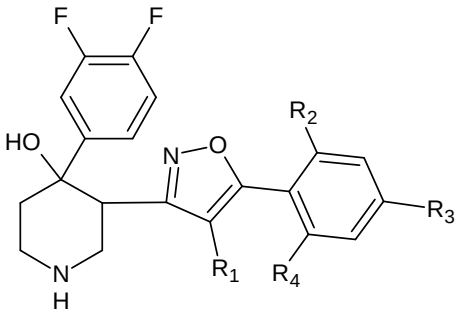
(62)



R=-CH_3, -C_2H_5, -C_3H_7

(63)

In an attempt to develop antihypertensives, Fournier *et al* [26] reported the synthesis of a novel isoxazolyl derivatives as renin inhibitor was subsequently been found to have shown sub-nanomolar renin inhibition even in the presence of human plasma.



R_1=Br, Cl, acetyl, 1-hydroxyethyl

R_2=C_2H_4NHAc, Cl

R_3=F

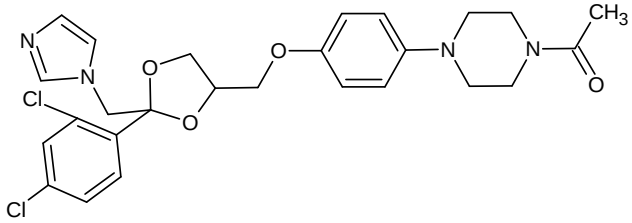
R_4=Cl

(64)

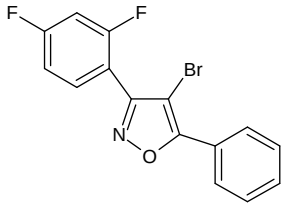
Compound (64), exhibited superior renin potency. Unfortunately, the extent of TDI observed was not improved with (64).

Shetty *et al* [27] reported the microwave assisted Suzuki synthesis of few 3,4,5-triarylisoxazole derivatives and screened for their antifungal activity against

Aspergillus flavus, *Fusarium oxysporum* and *Candida albicans*. Ketoconazole (65) was used as the reference antifungal agent.



(65)



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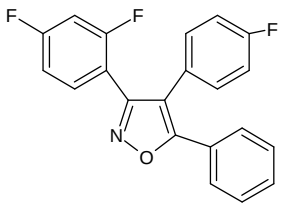
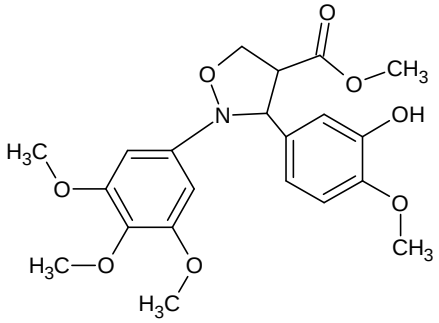


(67)

Compounds (66) and (67) exhibited highest antifungal activities against *F. oxysporus* and *C. albicans*.

2, 4, 5-trisubstituted isoxazoles

Kaffy *et al* [10] reported the synthesis of few novel combretastatin analogues bearing various five-membered heterocycles with consecutive oxygen and nitrogen atoms, in place of the olefinic bridge of CA4. These compounds were evaluated for cytotoxicity and their ability to inhibit the tubulin assembly.

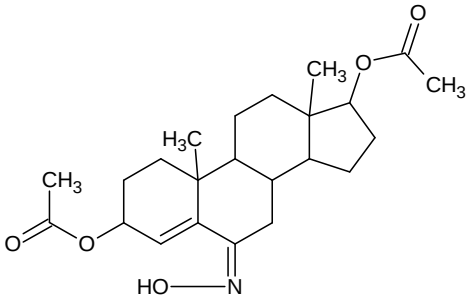


(68)

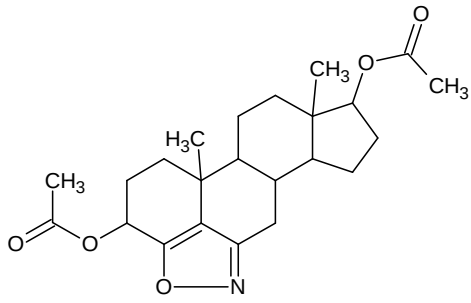
Compound (68) was found to be the most active one.

Fused ring system

Li *et al* [28] reported the rearrangement of steroidal oxime (69) to several isoxazolyl steroidal intermediates (70) to (73) potent inhibitors of human placental aromatase.



(69)



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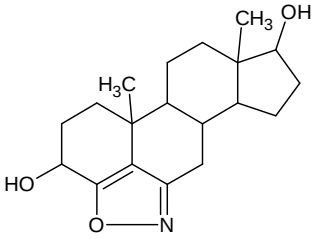

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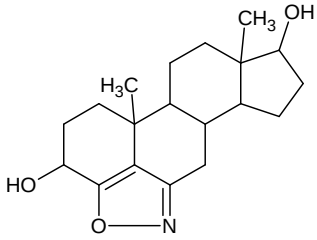

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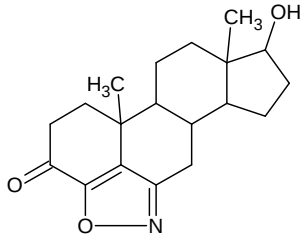
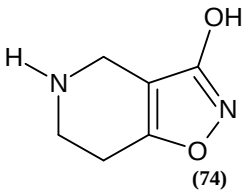
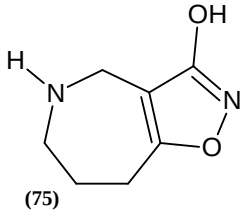


(73)

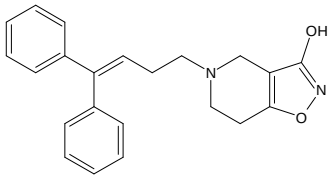
For the proper design and development of new GABA analogues of restricted conformation with the aim of producing novel anticonvulsant and antiepileptic drugs, Bolvig *et al* [29] studied the inhibitors of GABA transport and in particular as-troglial uptake such as 4,5,6,7-tetrahydroisoxazolo(4,5-c) pyridin-3-ol (76) and 5,6,7,8-tetrahydro-4H-isoxa-zolo(4,5-c)azepin-3-ol (77), which can act promising anticonvulsant agents.



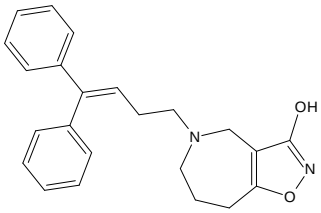
(74)



(75)



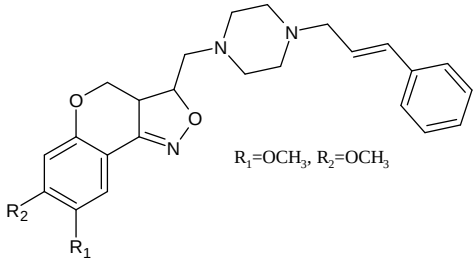
(76)



(77)

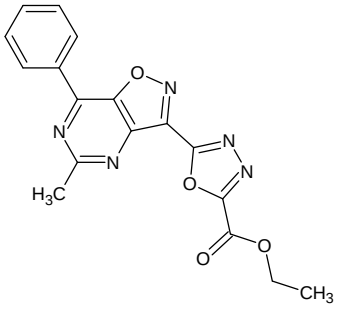
They tried to characterize the kinetics of THPO (74) and THAO (75) as well as their lipophilic 4,4-diphenyl-3-butenyl (DPB) derivatives in cultured neurones and astrocytes as well as at the cloned GABA transporters expressed in HEK 293 cells.

Andres *et al* [30] discovered a new series of 3-piperazinylmethyl-3a,4-dihydro-3H-[1] benzopyrano[4,3-c]isoxazoles (78) as novel dual 5-HT uptake inhibitors and α_2-adrenoceptor antagonists.

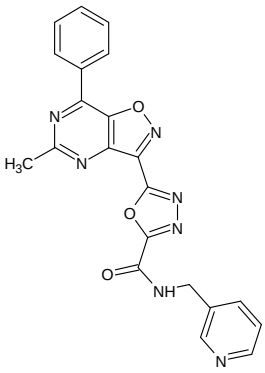


(78)

Wagner *et al* [31] reported the synthesis of isoxazolo[4,5-d]pyrimidine considering the structure of purine. It was observed that compounds (79) and (80) significantly inhibited the humoral immune response *in vivo* to sheep erythrocytes at a dose of 100mg.

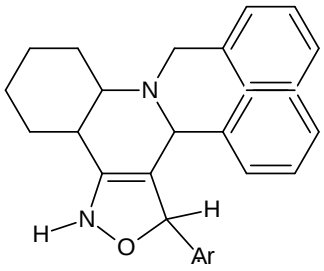


(79)



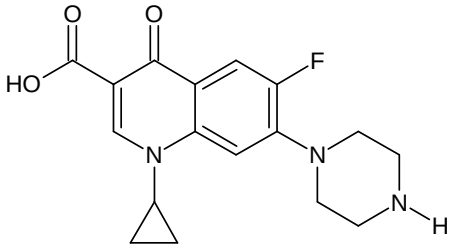
(80)

Mariappan *et al* [32] proposed the synthesis of a series of isoxazoloquinoline derivatives (81) and screened them for their antibacterial activity against six bacterial strains viz; *Pseudomonas aeruginosa* (ATCC 9027), *Escherichia coli* (ATCC) 35218, *Salmonella typhi* (ATCC 6539), *Staphylococcus aureus* (ATCC) 6538, *Bacillus subtilis* (ATCC6631) and *Bacillus shaericus* (ATCC 7031) by disc diffusion method using MH medium (MuellereHinton medium) and anti fungal activity against *Candida albicans* (ATCC 90028), *Aspergillus niger* (ATCC 16404) and *Aspergillus fumigatus* (ATCC28212) by agar cup plate method. Ciprofloxacin (82) (the antibacterialdrug) and Ketoconazole (65) (the antifungal drug) were used as reference standards.



Ar=Phenyl
o-Chlorophenyl
m-Nitrophenyl
p-anisyl
p-Chlorophenyl
2-furyl
5-Benzdioxole
2/3-pyridyl

(81)



(82)

Preliminary evaluation prompts them for further investigation.

CONCLUSION

Great strides were made in improving the quality of life of individuals affected with so many disorders. Isoxazole, while being present with various molecular fragments have shown a huge array of therapeutic benefit. Considering its chemical and clinical diversity, numerous novel compounds can be made as this review have given us a deep and extensive insight into the salient feature of isoxazole chemistry. Our future study aims at developing a robust bonding skeleton which may be useful in exploring several other unexplored targets.

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