REVIEW ON THE SYNTHESIS AND POTENTIAL THERAPEUTIC APPLICATIONS OF HETEROCYCLIC PRODUCTS OF 5-AMINO-3-METHYLISOXAZOLE

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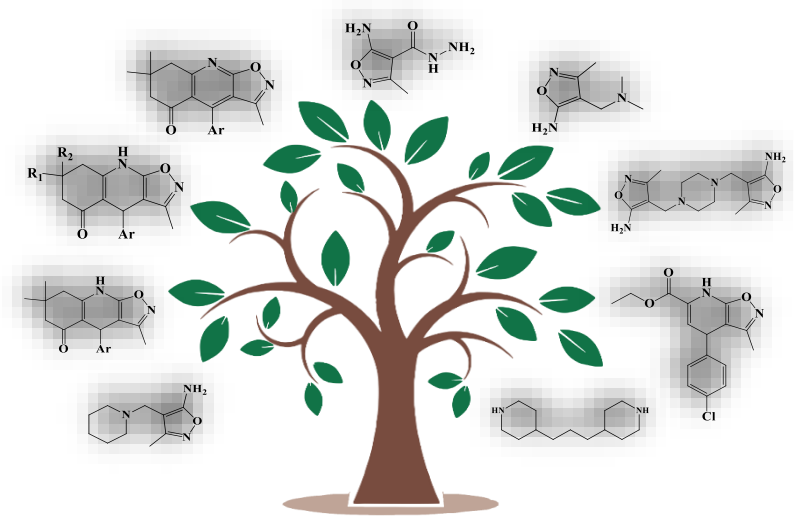
Abstract

In general, heterocyclic compounds have evoked interest and concern because of their fundamental role in biological profiles and biological actions in nature. Now, most of the lead molecules in medicinal chemistry are based on hetero-atoms. In medicinal chemistry- to bring two hetero-atoms to the drug molecule, isoxazoles are interesting functional groups. Isoxazole as a key building block has been widely used and is an important heterocyclic unit. Its derivatives attribute some functional activities in disorders like Alzheimer's disease, schizophrenia and hypertension, as well as have numerous pharmacological properties, like analgesic, antibacterial, hypoglycemic, anti-HIV, etc. Among the isoxazole derivatives, 5-amino-3-methylisoxazole have significant interest because it is starting material used to introduce isoxazole ring on the lead molecule and an important intermediate in medical chemistry. On the basis of the character & position of the substituent, 5-amino-3-methylisoxazole[5,4-d]4-pyrimidinone exhibited differential inhibitory activities, and acts on the initial phases of the immune response. Immunomodulatory properties of 5-amino-3-methyl-4-isoxazolecarbohydrazide were demonstrated. The effective immuno-suppressive action of this compound is showed in in-vitro assays. On the other hand, DFT (Density Functional Theory) reveals some molecular properties of isoxazole derivative which has been investigated earlier. To discover the potential medicinal use of this substance, further studies are required. The review aims at highlighting the synthesis of heterocyclic products of 5-amino-3-methylisoxazole and potential therapeutic use of isoxazole derivative.

Keywords: Isoxazoles, 5-amino-3-methylisoxazole, heterocyclization, microwave irradiation, Immunomodulator, B and T lymphocyte subsets, multicomponent reactions, eco-friendly.

Graphical Abstract: ***Heterocyclic Derivatives of 5-amino-3-methylisoxazole***



1. INTRODUCTION

Generally, heterocyclic compounds have evoked interest and concern because of their fundamental role in biological activity and biological actions in nature[1]. To efficiently design and synthesize biologically active molecules and new heterocyclic compounds with potential chemotherapeutic activities are the key challenges of topical chemistry[2, 3]. The demand for new testing compounds has tremendously increased by the discovery of high-throughput screening and, therefore, MCRs (multi-component reactions) became progressively useful tools to synthesize biologically active compounds as MCRs can dramatically lessen the production of chemical waste[4]. One-pot processes, in which 3 or more than three components react in a single reaction vial, to build a complex target product bearing essential elements in regards to all the reacting substances[5]. This methodology affords a molecular variety in a one-pot transformation and owing to their integrity, efficiency and high specificity it is broadly applied in medicinal chemistry, drug discovery and drug design[6]. MCRs allows exciting heterocyclic formworks, especially beneficial in combinatorial chemistry as prevailing tools[7], due to their precious characteristics e.g., environmental concerns, atom economy, the straight-forward reaction project, and the possibility to build desired compounds by introducing diversity of elements in one chemical operation[8]. Consequently, multi-component reactions aided by the microwave in the absence of

solvent might be considered as a potent green alternate to conventional synthetic operations. Among all isoxazole derivatives, 5-amino-3-methylisoxazole are of significant interest because it is used to introduce isoxazole ring as a starting material on lead molecule and an important intermediate in medical chemistry.

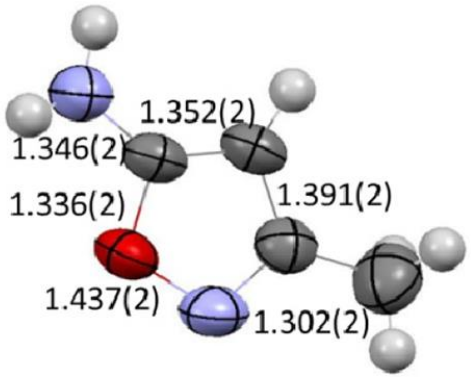


Image 1: Thermal vibrational representation of atoms of 5-amino-3-methylisoxazole of 50% probability

Spirooxindole core has manifold biological profiles and it is an exclusive heterocyclic ring system present in the majority of synthetic or natural compounds. Hence, this reaction gained enormous attractiveness from both medicinal and synthetic chemists[9]. Their prospective properties give rise to many attempts towards modification of the economic and cost-effective synthetic methods for the development of spirooxindole-fused heterocycles[10]. The spirocyclic oxindole are important scaffolds in drug discovery and synthesized on the basis of variable reactivity of isatins have significantly attracted synthetic chemists[11]. Particularly, these scaffolds having a quaternary stereocenter at position-3 exhibit potential biological actions and through suitable synthetic strategies, its stereo-chemistry must be controlled. Moreover, to complement the flat hetero-cyclic compounds, the 3D shape of spirooxindoles is a captivating target found in many drug discovery schemes[12].

Because of exciting pharmacological and biological properties, Isoxazoles derivatives have widely attracted the attention of chemists[13]. They have wide concern as synthetic halfway in the synthesis of many organic compounds[14] and chiral ligands[15]. Generally, isoxazoles are distinctive in their chemical behavior in the group of the related azoles and are the main class of hetero-aromatic molecules[16]. Some of them have been registered as drugs and some were found to be generally applied in medicine. Isoxazoles are the main constituent of diverse natural products and medicinal compounds[16] e.g., valdecoxib[17] and ibotenic acid[18]. Due to the liquid crystalline property exhibited by isoxazoles, these compounds are potentially applied in opto-electric devices[19].

HIX also known as 5-amino-3-methyl-4-isoxazolecarboxylic acid hydrazide has a pharmacophore structure is mainly used to synthesize a group of derivatives of isoxazole with immuno-modulatory functions. The pharmacologic attributes of that compound on cellular immune reactions are reported in vitro [20]. Moreover, many applications of isoxazoles functionalized possessing an additional N-containing group have observed in literature[21].

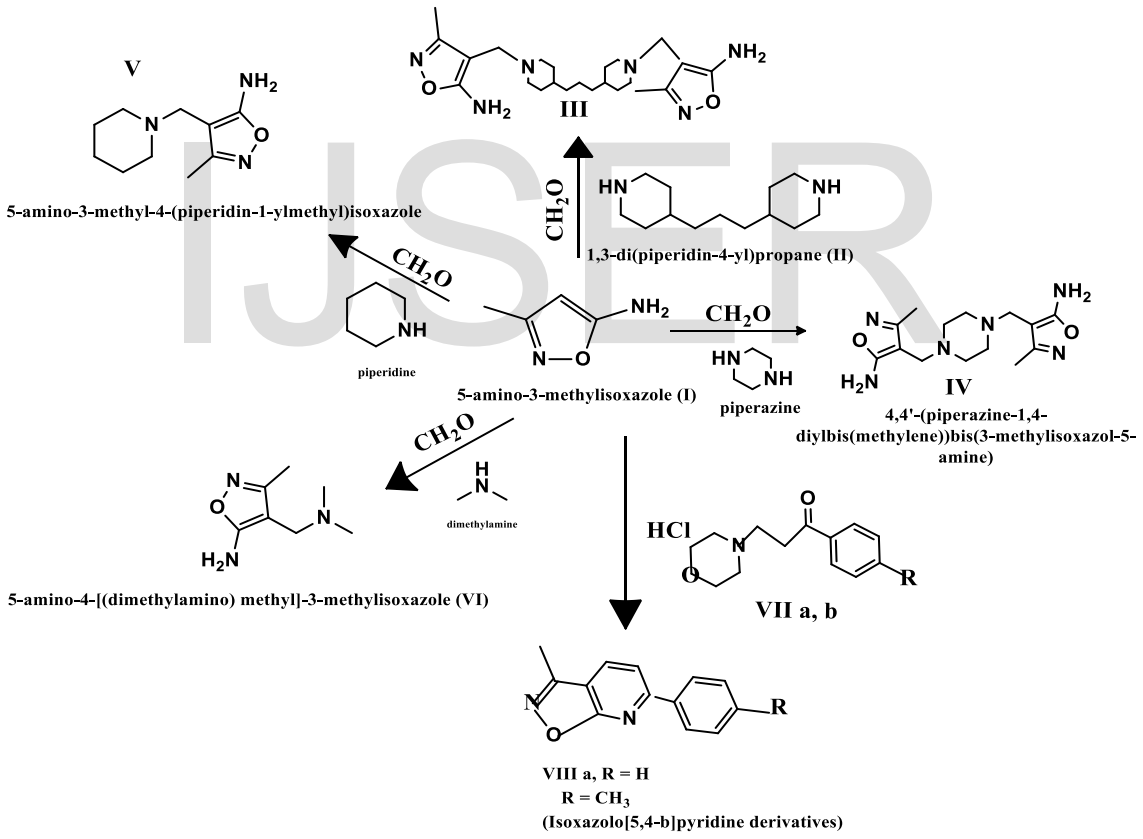
Aminoisoxazole is a prime versatile reagent in current heterocyclic chemistry and is considered as 1, 3-binucleophiles (as exocyclic heterocyclic enamine) by its reactions with electrophilic compounds[22].

A considerable research efforts in pharmaceutical industry & academic circles is concerned with treatment of cancer in recent years because it is considered as the major reason of death. Therefore, novel potential drugs are synthsized by using isoxazoles as synthon as present anticancer agents were seem to posses lethal side effects such as toxicity, drug-resistance and reduced bio-availability[23-26]. Because of problems related to currently available anti-cancer medicine or drugs, considerable attention has been attributed to the search of anticancer agents[27]. For the preparation of the bioactive O- & N-containing heterocyclic compounds, great efforts

towards the development of synthetic routes to get functionalized heterocyclic compounds have been intended[28]. Some isoxazoles bearing a basic side chain have been prepared that would produce effective anti-cancer actions.

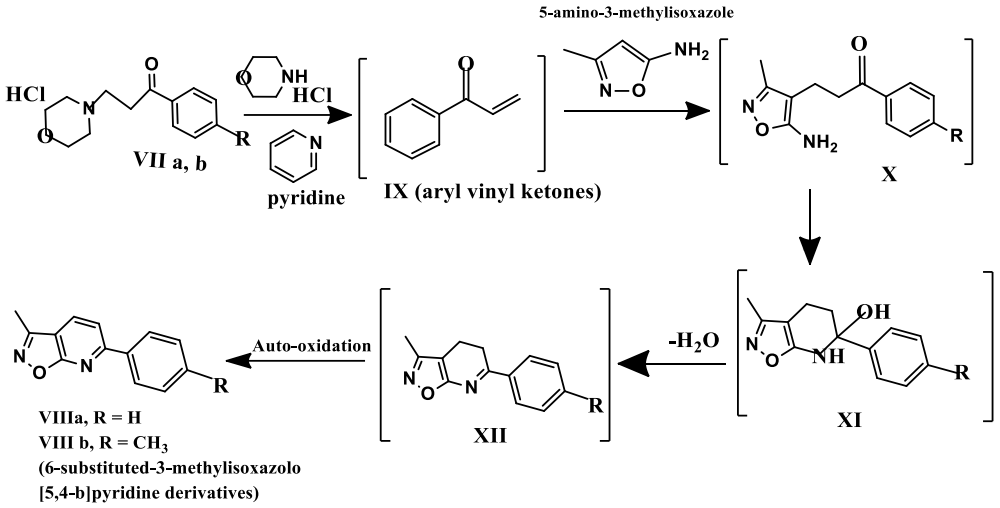
1.1 Chemistry

By investigating the action of 5-amino-3-methylisoxazole **(I)** in Mannich reaction, it is reported that it acts as an enamine when it reacts with **II** (dibasic 2º-amine) and formalin in 2:2:1 (molar ratio) to yield **(III)** and with piperazine to yield **(IV).** In addition, the Mannich reaction of **I** with a mixture of piperidine (monobasic 2º-amines) and formalin in 1:1:1 yielded **(V)** and with dimethylamine to afford corresponding **(VI)**. Unsubstituted ring system of **VIII** have been sythesized by alkylation at position-4 with Mannich bases. Moreover, the reacting 5-amino-3-methylisoxazole with **(VII a or b)** in pyridine (refluxing), respectively produced the products (a) & (b) by condensation reaction. The manufacturing of isoxazolopyridines **VIII(a) & VIII(b)** is because of the unstability of β-aminopropiophenones to yield non-isolable aryl vinyl ketones[29, 30].



Scheme 1: Formation of compounds of isoxazole with a basic side chain and derivatives of VIII (a), (b)

Aryl vinyl ketones which is formed experience an intermolecular Michael addition of beta-carbon of an exocyclic enamino group of 5-amino-3-methylisoxazole to the carbon-carbon double bond of an **(IX)** to produce the intermediate **(X)** undergoes intramolecular cyclization to generate **XI (**a non-isolable intermediate**)** with the release of a H_2O to yield the **(XII)** subsequently undergoes auto-oxidation[31].

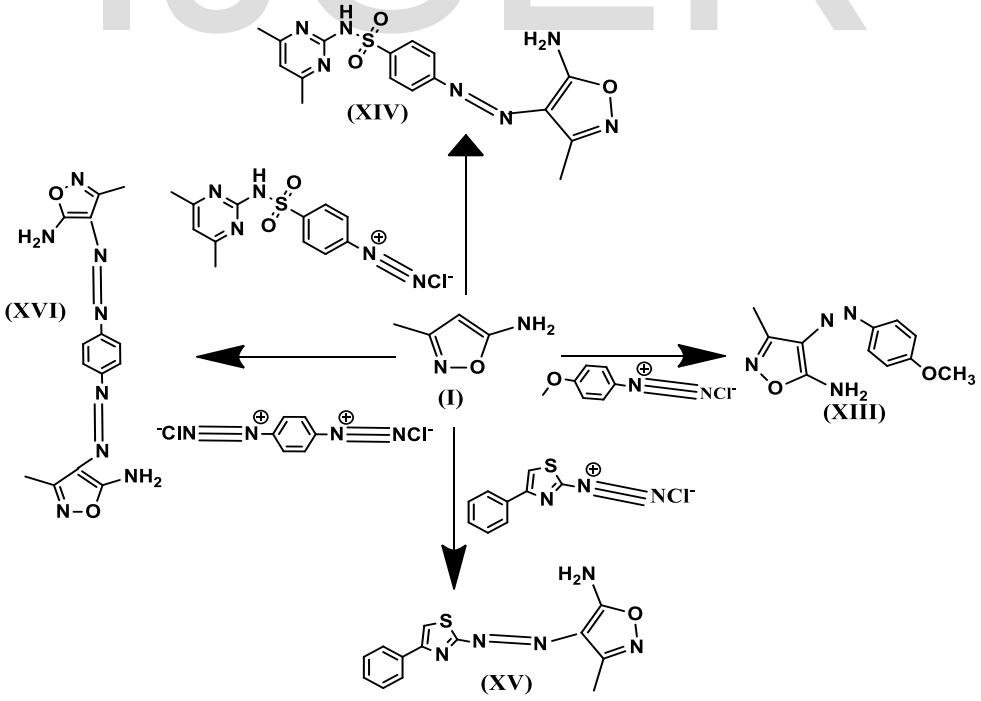


Scheme 2: A mechanism of the synthesis of derivatives of VIII (a) & (b)

1.2 Coupling reaction of (I)

It is noted for many years that dye compounds were used widely in high-technology sectors such as electro-optical devices, lasers and liquid crystalline. Dyes were considerably used for dyeing textile fiber and have numerous applications in organic synthesis and biomedical fields[32, 33].

The coupling reaction of various diazomium salts of 1º aromatic amines e.g., 4-amino-N-(4,6-dimethylpyrimidin-2-yl)benzene sulfonamide, p-anisidine, p-pheylenediamine or 2-amino-4-phenylthiazole with 5-amino-3-methylisoxazole yields the corresponding dyes XIII-XVI, respectively [34].



Mono-isoxazole and bisazo-isoxazole derivatives (XIII - XVI).

Scheme 3: The schematic representation of the synthesis of azo-isoxazole derivatives (XIII - XVI)

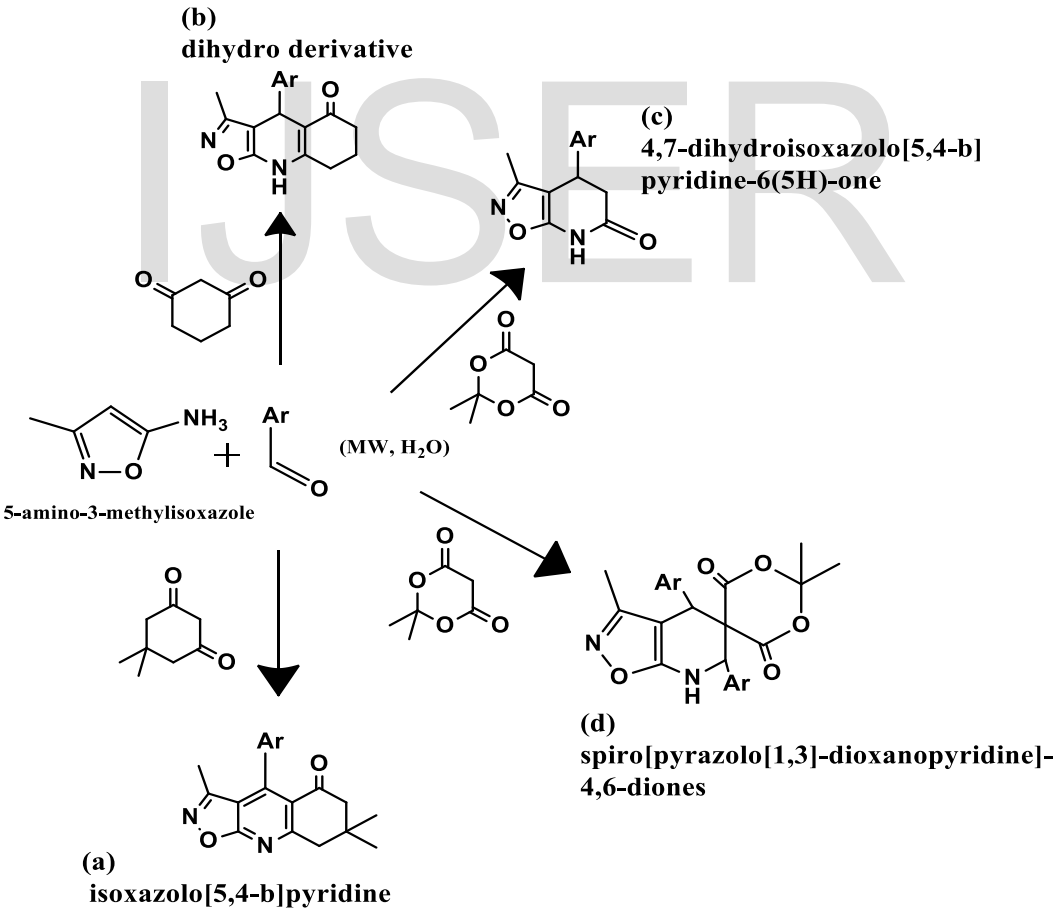
1.3 Multicomponent reactions (MCRs)

Three-component heterocyclizations of cyclohexanedione derivatives, (I) and salicylic aldehydes, under microwave irradiation, ultrasonication, conventional thermal heating have been studied to selectively synthesize 6,7,8,9-tetrahydroisoxazolo[5,4-*b*]quinolin-5(4*H*)-ones and 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones[35].

1.3.1 Microwave-assisted three- component reaction with several active methylene compounds

Microwave-assisted reaction of three components e.g., aldehydes, respective active methylene compounds (1,3-cyclohexanediones, tetronic acid, 1,3-indanedione and Meldrum's acid) and 5-amino-3-methylisoxazole are reported while the reaction in which dimedone is involved, it yield **(a)** while with 1,3-cyclohexanedione the ultimate product was **(b)**.

(c) is formed by ring-opening in condensation with Meldrum's acid, meanwhile $(CH_3)_2CO$ & CO_2 are released. [36] Though, in another article another Tu and co-authors reported the reaction of Meldrum's acid with (**I**) and aldehydes under similar circumstances produces **(d)** rather isoxazolopyridinones[37].

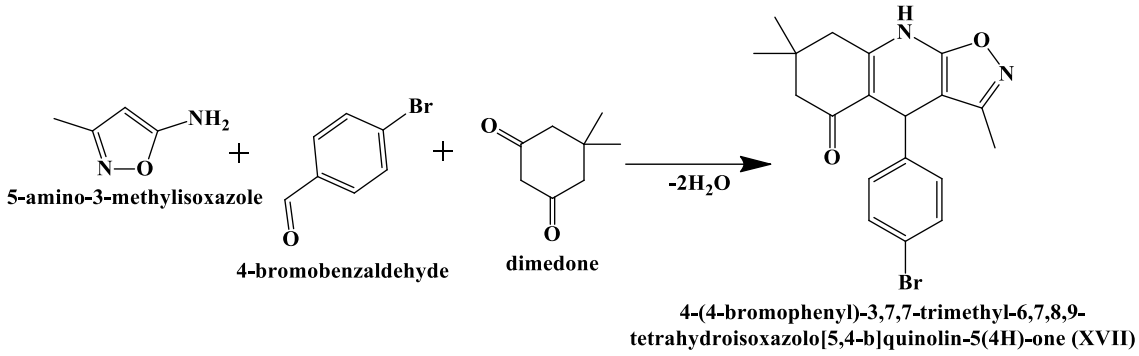


Scheme 4: Some well-known MCRs involving 5-amino-3-methylisoxazole

Furthermore, the one-pot reaction of aromatic aldehydes, (**I**) with 2-hydroxy-1,4-naphthoquinoneafforded benzo [*h*]isoxazolo[5,4-*b*]quinoline-5,6-diones[38].

1.3.2 The MCR between (I), 4-bromobenzaldehyde, & dimedone

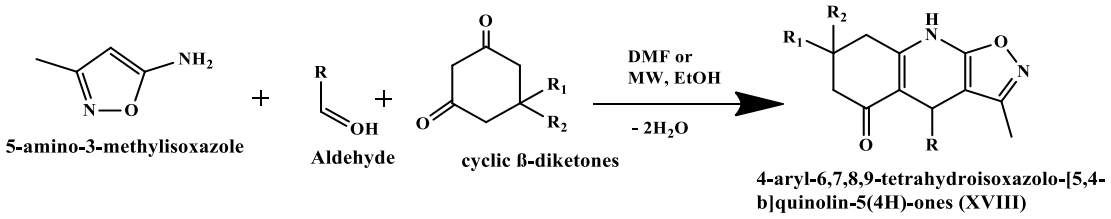
The multi-component reaction of dimedone, **(I)** & 4-bromobenzaldehyde gives **(XVII)** with yields from 50% for ethanol to 75% for dimethylformamide with the purity about 95% with formal heating (Δ) of the reactants in solvents such as water, ethanol and DMF. It was found that the excellent yields (~90%) of the compound with high purity irrespective of the solvent type, were observed when the multi-component reaction proceeds under microwave irradiation (MW) at 120°C.



Scheme 5: Optimizating the conditions of 3-component (one pot) reaction between dimedone, (I) & 4-bromobenzaldehyde

1.3.3 Multi-component reaction of cyclic *β*-diketones, (I) & aldehydes

MCRs between aldehydes, cyclic *β*-diketones and (I), in boiling dimethylformamide gives **(XVIII)** in 55-91% yields. It should be notable that in most of the cases the microwave-assisted procedure and application of microwave activation produces the best results and desired targets with respect to the yields and purity of the end product than conventional heating[35].



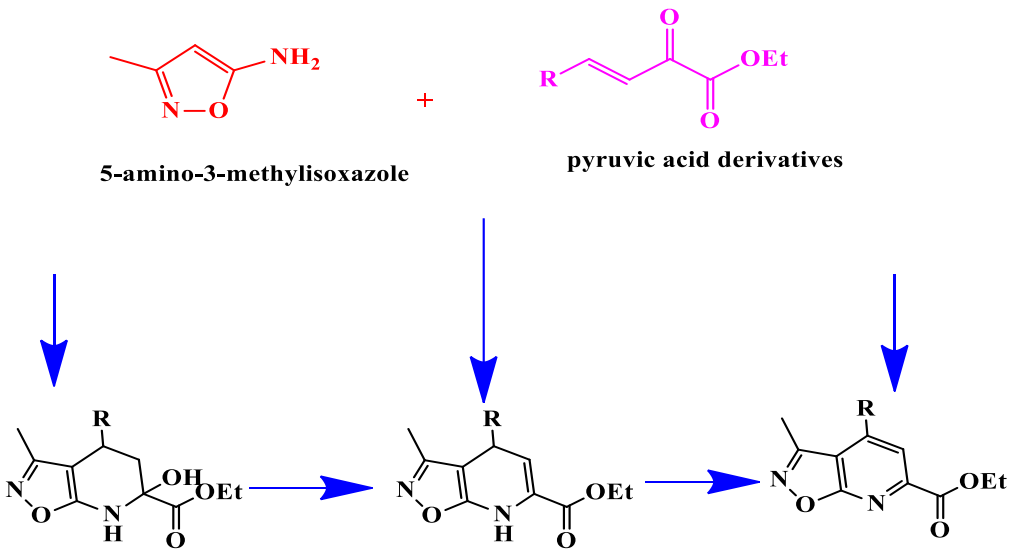
Scheme 6: The Multicomponent microwave-assisted synthesis of XVIII

1.3.4 Two-component heterocyclization reaction of pyruvic acid derivatives & (I)

A two-component reaction of pyruvic acid derivatives and 5-amino-3-methylisoxazole by using both the microwave irradiation & ultrasonication alongwith the traditional methods of activation have been reported [39]. It was found that in the heterocyclizations, only NH_2-substituent of **(I)** interacts with pyruvic acid derivative and thus the interactions of esters of arylidene pyruvic acids yields three different types of heterocyclic systems[39, 40].

In two- & multi-component reactions, 5-amino-3-methylisoxazole is not stable with pyruvic acid & its arylidene derivatives. However, with ethyl 4-aryl-2-

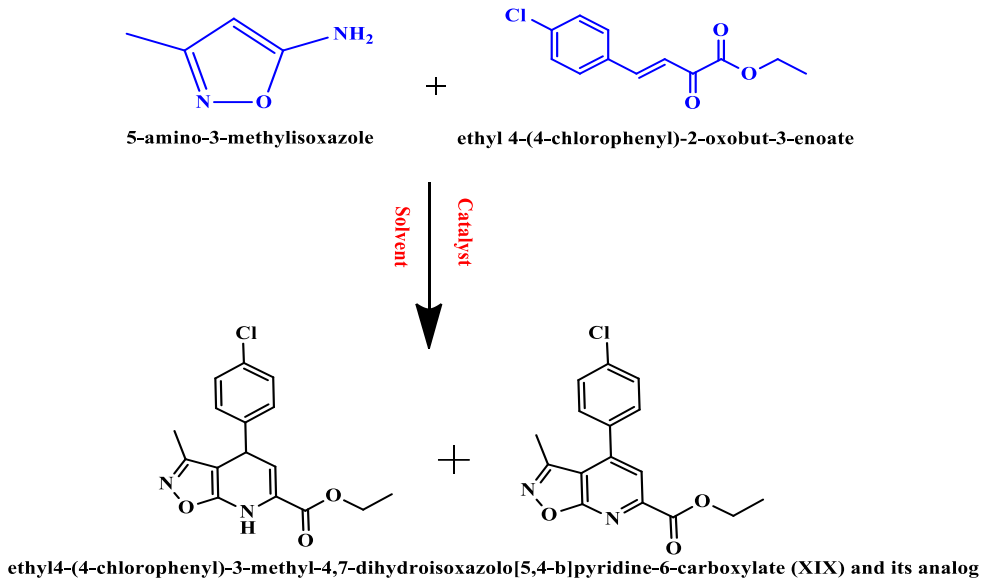
oxobut-3-enoate in two-component condensations with $Sc(OTf)_3$ yields not only isoxazolo[5,4-*b*]-pyridines, but also both di- & tetrahydropyridines[41].



Scheme 7: Some products of heterocyclization involving (I)

The interaction of ethyl 4-(4-chlorophenyl)-2-oxobut-3-enoate & **(I)** in refluxing ethanol or methanol results in decomposition of 5-amino-3-methylisoxazole, but no reaction products can be isolated. However, when refluxed in toluene, dichloromethane or acetonitrile allowed to get only unaltered reacting substances from the solution. The reaction in C_2H_5OH in glacial acetic acid or with the catalytic amount of HCl at different temperatures consequently results in tarring of the reaction mixture. Using Lewis acids as catalysts, is one of the well known practise to improve the reactivity of α,β-unsaturated compounds (carbonyl compounds)[42-44].

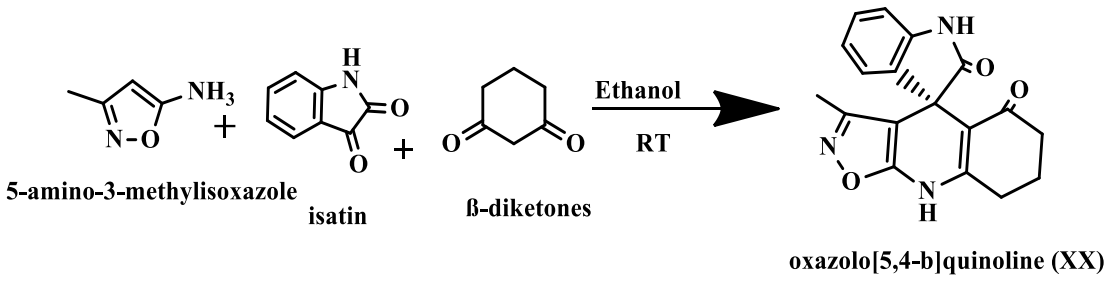
The electron density shift toward oxygen in the conjugated C=C–C=O system evidences to increased the electrophilic attribute of C-atom at the beta-position. Whenever ytterbium triflate-$Yb(OTf)_3$ which is water-soluble Lewis acids, were used as catalysts, a mixture of **(XIX)** and its heteroaromatic analog are produced, even refluxed in acetonitrile. The yield and selectivity of target compounds is enhanced by applying microwave irradiation. It was noted that yield of products can also be enhanced by increasing the temperature from 80-100°C. Thus, the yield of **(XIX)** can be improved to 73% and that of its heteroaromatic analog to 11%[39].



Scheme 8: A scheme representing the synthesis of a mixture of (XIX) and its heteroaromatic analog

1.4 Cycloaddition reactions

To synthesize 3-spiropyrrolidine-3-spirooxindoles by a [3+2] cycloaddition, the efficient and simple procedure have recently been reported[45]. On the basis of the development of new & selective, environmentally friendly methodologies for the synthesis of spiro-heterocyclic compounds, many efforts were made to form oxazolo[5,4-b]quinoline by the one-pot reaction with three components which are isatin, **(I)** & β-diketones by refluxing in C_2H_5OH. However, by reacting β-diketones, isatin & **(I)** at room temperature in C_2H_5OH gives 30% of desired products in the aspect of chemo-selective. Several spectroscopic analyses (^{1}H-NMR, mass spectroscopy, ^{13}C-NMR, and DEPT-135) are applied to verify the structure of **(XX)**[12].



Scheme 9: The one-pot synthesis of (XX) – a fused spirooxindoles

The different factors that effect the reaction are temperature range, different solvents, and time. These have been subsequently studied. ***(Table 1)***

Table 1: Optimizing the conditions for the formation of (XX) under MW irradiation[a] [12]

Sr no.	Temp.	Solvents	Time (hours)	% Yield[b]
1	RT	Water	7	NR
2	RT	Ethanol	8	30
3	RT	Methanol	8	20
4	80	Toluene	6	70
5	60	Ethanol	7	65
6	50	Acetonitrile	6	50
7	120	No solvent	2	80
8	110	No solvent	10 (min)	95

[a] Conditions for reaction: 1 mmol isatin, 1 mmol (I), & 1 mmol β- diketones were irradiated at 700 Watt for ten minutes in a microwave reactor.

[b] Isolated yield

Thus, it is concluded that the best condition for this transformation is microwave irradiation under the solvent-free condition[12].

1.5 Pharmacology

In medicinal chemistry, isoxazole derivatives possesses some valuable activities in conditions like schizophrenia, Alzheimer's disease and hypertension, as well as contains many pharmacological properties, for example analgesic, antibacterial, hypoglycemic, anti-HIV, anti-inflammatory & anti-cancer activity. Among the isoxazole derivatives, 5-amino-3-methylisoxazole have significant interest because 5-amino-3-methylisoxazole is starting material used to introduce isoxazole ring on lead molecule and an important intermediate in medical chemistry.

In recent years, the effect of substituted 5-amino-3-methylisoxazole based substances on the practicality of Ehrlich ascites carcinoma (EAC) cells were reported in vitro.

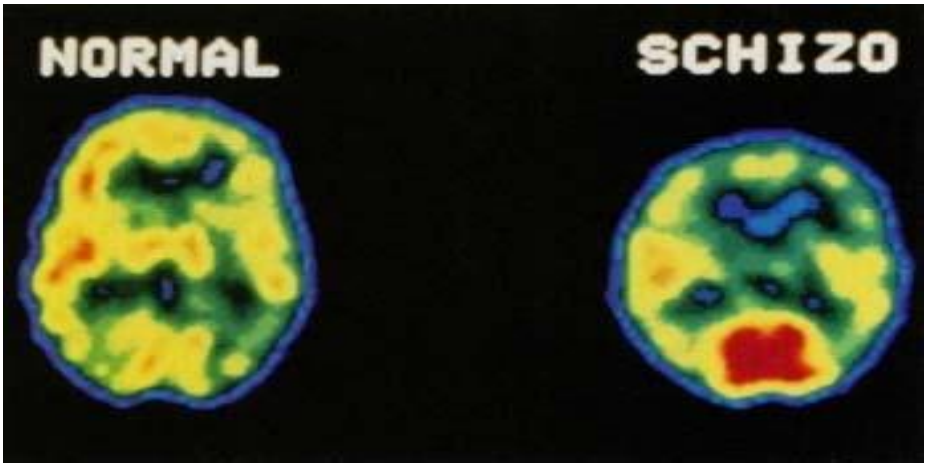


Image 1: Normal v/s schizophrenia brain

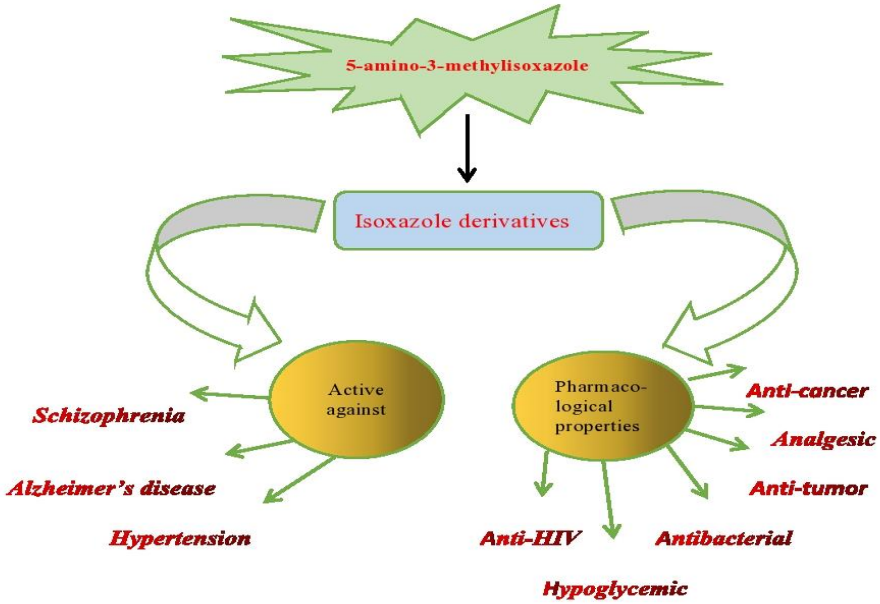


Image 2: Schematic representation of therapeutic uses of 5-amino-3methyl-isoxazole

1.5.1 Anti-tumor activity

Almost 10 derivatives of isoxazole were tested for their prospective anti-tumor activity against EAC cells in vitro[46]. Following Table 1 consist the results of active compounds for IC_{50} values. The table 1 data clearly reveled that compounds **III, IV, V, XV, VIIIa and VIIIb** exhibited high anti-tumor activity compared with 5-fluorouracil, respectively while compounds **XIII, XIV,** and **XVI** exhibited lower anti-tumor activity than 5-fluorouracil. Moreover, the results which are mentioned before reveals the following structure activity relationships (SAR):

(i) anti-tumor activity could be increased with the presence of ring systems of thiazole and fused pyridine; **(ii)** anti-tumor activity also increases by the presence of piperazine moiety;[47] **(iii)** anti-tumor activity in the compound 3 increases by introducing the basic side chain the;[48] **(iv)** moreover, the presence of azo or bisazo moieties lower cyto-toxic activity of dyes compounds **XIII**, **XIV**, and **XVI**.[31] The test compounds with different concentrations were tested for metabolic activity of the cells by means of trypan blue assay. ***(Table 2)***

Table 2: In vitro, latent antitumor activity of isoxazole analogues using EAC assay [31]

	% Dead[a]		
Comp. No.	100 µg/mL	50 µg/mL	25 µg/mL
8a	77.4 c/o	42.7 c/o	24.2 c/o
8b	59.8 c/o	34.6 c/o	19.0 c/o
16	34.9 c/o	22.0 c/o	13.3 c/o

15	95.8 c/o	77.0 c/o	48.6 c/o
14	25.0 c/o	14.8 c/o	7.0 c/o
13	26.1 c/o	12.3 c/o	5.7 c/o
6	71.9 c/o	38.7 c/o	21.8 c/o
5	82.4 c/o	49.8 c/o	29.0 c/o
4	68.2 c/o	38.0 c/o	21.6 c/o
3	76.0 c/o	41.3 c/o	23.0 c/o
5-Fu[b]	98.1 c/o	68 c/o	37.7 c/o

[a]: The % of the dead tumor cells.
5-Fu[b]: is 5-fluorouracil - a well-known cytotoxic agent.
c/o : Complaining of - is a medical term.

1.5.2 Anti-cancer activity

A large number of isoxazole compounds are synthesized possessing potential anticancer activity by some modification or alteration of isoxazole derivatives. On the basis of preliminary screening results, compounds **III, XV, IV, VIIIb, V** and **VIIIa** showed significant anti-tumor activity in certain cancer cells. To set relative activity for SAR and rational design, various additional researches, including the mode of action are planned[47]. Studies to analyze the compounds with apoptosis inducing activity and those possessing high anti-tumor activity are underway[31].

1.5.3 The effect of (HIX) on humoral immune response & lymphocyte subsets

The working of immune system depends upon how efficient its all components are & their intractability to T $CD4^+$ of lymphocytes. To collect the data about the working of body tissues & to show primary immune proficiency are the main functions of these cells. Lack of this population of T cells either quantitative or qualitative leads functionally subordinated immune cells to secondary dysfunction of that may be obvious by an enhanced incidence of infections, the occurrence of allergic diseases & autoimmune, a decrease of anti-tumor immunity or hematopoietic disorders.

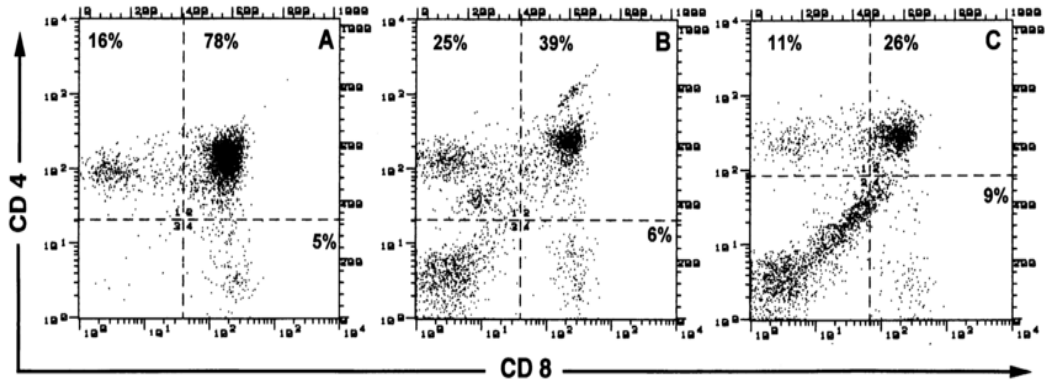


Image 3: Representative flow-cytometric analyses of thymocyte subpopulations following wild-type Chi-1 MV infection. Thymocytes were analyzed for expression of CD4 and CD8. (A) Mock-infected implant. Thymocytes from Thy-Liv implants 7 days (B) and 10 days (C) following Chi-1 infection are shown.

Immune-mediated disease is a significant challenge for today's drugs. Therefore, the search for substances efficient for altering the functional status of the immune system is necessary. Five-membered isoxazole ring derivatives gain special attention together with the substances which are prepared by the chemical synthesis. By chemical synthesis, the molecule of well-defined & known structure with purity can be synthesized[49]. The reason to those research attempts is a possible sanative use of those compounds possessing such actions. The immunomodulators are substances of either synthetic nature (levamisole, imiquimod) or natural (bacterial adjuvants, thymic hormones, plant secondary metabolites, recombinant cytokines)[50, 51].

Isoxazole ring mainly 5-membered is the concerned object of both chemists and pharmacologists searching for new substances and studying their properties, respectively as the isoxazole ring is comparatively easily achieved by chemical synthesis. The succeeding derivatives of 5-membered isoxazole ring possesses many biological activities and exhibit therapeutic potentials[49]. These group of compounds have well-known effect on modulating the function of the immune system[52-54]. Some of their characteristic properties involve anti-convulsant activity[55], anti-inflammatory activity[56], and an suppression of HIV protease activity[57], an inhibition of estrogen synthase[58].

HIX are molecular key structure to synthesis bunches its derivatives which are biologically active and series of semicarbazides and thiosemicarbazides having immunotropic activity[60 ,59]. HIX were found to have diverse activities but they usually were immunomodulatory and anti-inflammatory ones[61]. **HIX** can alter the entire % and no. of T and B lymphocytes in the peripheral lymphatic organs and T lymphocytes in the thymus. These changes depends on treatment- and dose-duration.

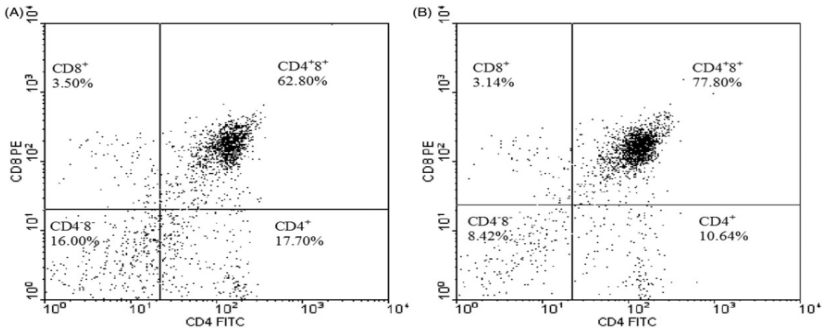


Image 4: Thymocyte subpopulations – examples of dot plots. (A) Control group. (B) HIX applied once with the quantity of 0.1 mg/kg (after 72 hours).

The *N*'-substituted hydrazides of HIX which exhibit inhibitory activities, substituted thiosemicarbazides & semicarbazides of HIX [62, 63], with immunomodulatory properties, 5-substituted 3-

methylisoxazolo[5,4-d]pyrimidin-4-one derivatives[61] which were found to have inhibitory activities, 5-substituted 3-methylisoxazolo[5,4-d]-[1],2,3-triazine-4-one derivatives[61] also exhibit inhibitory properties were prepared by using HIX substrate[64]. Because of the stimulating actions, HIX found to be worthy immune response modifier that presumably used potentially against some bacterial & viral infections or as an ''adjuvant'', which is a compound used with vaccines which manifolds the cellular or humoral immune response to an antigen and aid to save the cost of vaccines by reducing the quantity of wanted antigen[65]. Additionally, some recent studies showed that the hydrazide exerts no cyto-toxic effects,[66] which is a characteristic feature of 'adjuvants' in the viewpoint of their safety.

Location and character of the substituted groups affect the immunomodulatory effects of reported substances, these effects are diverse and influenced their discriminatory suppression of the cellular and humoral immune response[61].

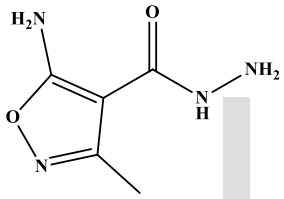
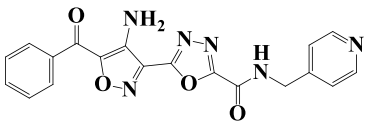


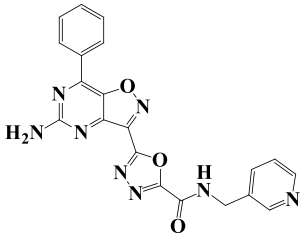
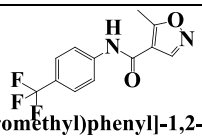
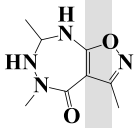
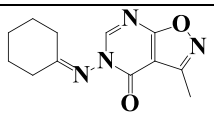
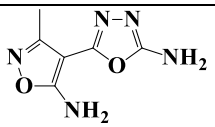
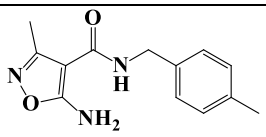
Image 5: The structural formula of HIX

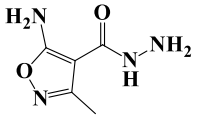
1.5.4 Immunosuppressive actions

A large number of derivatives of isoxazole under concentration demonstrate immunosuppressive activities, such as anti-inflammatory, there is little knowledge about immunostimulatory compounds that have potential therapeutic utility. Besides immunosuppressive molecules, these compounds were also produced and evaluated for their potential therapeutic utility by researchers[67].

Table 3: The potential activities of isoxazole derivatives in therapy

Compounds	Molecular/ Cellular Mechanism of Action	Activity	Ref. #
		Immunosuppressive actions	
 **5-(4-amino-5-benzoyl-1,2-oxazol-3-yl)-N-[(pyridin-4-yl) methyl]-1,3,4-oxadiazole-2-carboxamide**	Not defined	Inhibits the Proliferative response of mouse splenocytes to concanavalin A, suppresses the	[68]

		humoral immune response	
 5-(5-amino-7-phenyl[1,2]oxazolo[4,5-d]pyrimidine-3-yl)-N-[(pyridin-3-yl)methyl]-1,3,4-oxadiazole-2-carboxamide	Not defined	Stimulates Mitogen Induced proliferation of Mouse splenocytes, suppresses DTH	[68]
 5-methyl-N-[4-(trifluoromethyl)phenyl]-1,2-oxazole-4-car	COX-2 inhibitor	Supperesses T-cell-dependant B-cell responses, does not effect T-independent B-cell function	[69]
 3,5,7-trimethyl-5,6,7,8-tetrahydro-4H-[1,2] oxazolo[5,4-e][1,2,4]triazepin-4-one	Stimulation of caspase 9 expression in thymacytes and splenocytes and Fas in bone marrow cells and splendocytes, inhibitiob of ERK1 and p38 in bone marrow cells.	Inhibit LPS-induced TNF-α and IL-6 activity inhibits antibody production	[70]
 5-(cyclohexylideneamino)-3-methyl[1,2] oxazolo[5,4-d]pyrimidine-4(5H)-one	Not defined	Shows immunosuppressive property, lower polyclonal antibody production	[71]
 5-(5-amino-3-methyl-1,2-oxazol-4-yl) -1,3,4-oxadiazol-2-amine	Not defined	Inhibit the humoral immune response, the carrageenan reaction and proliferation of lymphocytes	[72]
 5-amino-3-methyl-N-[(4-methylphenyl)methyl]-1,2-oxazole-4-carboxamide	Inhibitor of TNF α production	Inhibits the humoral immune response in vitro	[73]

 5-amino-3-methyl-1,2-oxazole -4-carbohydrazide	Upregulation of fractalkine(CX3CL1) and IL-17F, and Downregulation of IL-10and TLR4	Modulates the content of Tcell subsets and B cells in lymphoid organs, and elevates the humoral immune response in mice	[74]

Conclusion

Isoxazoles acts as fundamental building block and is an important heterocyclic unit. A large number of compounds of isoxazole with possible anticancer activity are synthesized by some modification of derivatives of isoxazole. A series of low M.W. immune modifiers have become profoundly valued therapeutic agents. The heterocyclic isoxazole structure has been used as the core for the synthesis of many potential drugs with varied biological activities. On the basis of these preliminary screening results, compounds **III, XV, VIIIb, IV, VIIIa,** and **V** possesses significant anti-tumor activity for certain cancerous cells, and it will be used for further studies.

5-amino-3-methylisoxazole derivative; **HIX** could modulate the action of the immune cells in vivo as well as in vitro. To establish relative activity for SAR and rational design, certain additional researches, including the mode of action are planned. However, studies about some compounds which exhibit the apoptosis inducing activity are underwent and these are the compounds that shows high anti-tumor activity in this article.

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