MEDICINAL CHEMISTRY RESEARCH

CrossMark

The synthetic and therapeutic expedition of isoxazole and its analogs

Neetu Agrawal[1] · Pradeep Mishra[1]

Abstract
Isoxazole, constituting an important family of five-membered heterocycles with one oxygen atom and one nitrogen atom at adjacent positions is of immense importance because of its wide spectrum of biological activities and therapeutic potential. It is, therefore, of prime importance that the development of new synthetic strategies and designing of new isoxazole derivatives should be based on the most recent knowledge emerging from the latest research. This review is an endeavor to highlight the progress in the chemistry and biological activity of isoxazole derivatives which could provide a low-height flying bird's eye view of isoxazole derivatives to the medicinal chemists for the development of clinically viable drugs using this information.

Abbreviations

5-HT	5-hydroxy tryptamine
A. clavatus	Aspergillus clavatus
A. fumigates	Aspergillus fumigatus
A. niger	Aspergillus niger
AChE	Acetylcholinesterase
AR	Adrenergic receptor
B. cinerea	Botrytis cinerea
B. subtilis	Bacillus subtilis
BBB	Blood-brain barrier
C. albicans	Candida albicans
C. elegans	Caenorhabditis elegans
C. neoformans	Cryptococcus neoformans
C. tropicum	Chrysosporium tropicum
CA	Carbonic anhydrase
CDK	Cyclin-dependent kinase
CK	Casein kinase
CNS	Central nervous system
COX	Cyclooxygenase
cyt	Cytochrome
D. myceliophagus	Ditylenchus myceliophagus
DGAT	Diacylglycerol acyl transferase
DPP	Dipeptidyl peptidse
DPPH	2,2-diphenyl-1-picrylhydrazyl
E. coli	Escherichia coli
E. faecalis	Enterococcus faecalis
E. floccosum	Epidermophyton floccosum
EC	Effective concentration
ED	Effective dose
ELISA	Enzyme-linked immunosorbent assay
EPAC	Exchange proteins directly activated by cAMP
FLAP	5-lipoxygenase-activating protein
FLT	FMS-like tyrosine kinase
FRAP	Ferric-ion reducing antioxidant power
FXR	Farnesoid X receptor
GABA	γ-amino butyric acid
HDAC	Histone deacetylase
HDL	High density lipoprotein
HMEC	Human microvascular endothelial cells
Hsp	Heat shock protein
HSV	Herpes simplex virus
HTS	High-throughput screening
IC	Inhibitory concentration
JNK	c-Jun N-terminal kinase
K. pneumonia	Klebsiella pneumoniae
L. donovani	Leishmania donovani
LDL	Low density lipoprotein
LPA	Lysophosphatidic acid
mAChR	muscarinic acetylcholine receptor

✉ Neetu Agrawal
kumkumagr.1990@gmail.com

[1] Institute of Pharmaceutical Research, GLA University, Mathura, U.P., India

MAO   Monoamine oxidase
MAP   Mitogen-activated protein
MBEC   Mouse brain endothelial cells
MES   Maximal electric shock
MIC   Minimum inhibitory concentration
MTB   *Mycobacterium tuberculosis*
MTT   3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide
nAChR   nicotinic acetylcholine receptor
P. aeruginosa *Pseudomonas aeruginosa*
P. chrysogenum *Penicillium chrysogenum*
PPAR   Peroxisome proliferator-activated receptors
PTP   Protein tyrosine phosphate
R. cerealis   *Rhizoctonia cerealis*
R. oryzae   *Rhizopus oryzae*
S. aureus   *Staphylococcus aureus*
S. pyogenes   *Streptococcus pyogenes*
S. typhi   *Salmonella typhi*
S. typhimurium *Salmonella typhimurium*
S1P   Sphingosine-1-phosphate
SAR   Structure-activity relationship
scPTZ   subcutaneous pentylenetetrazole
SIRT   Silent information regulators
sPLA   Secretory phospholipase A
STAT   Signal transducer and activator of transcription
T. mentagrophytes *Trichophyton mentagrophytes*
T. rubrum   *Trichophyton rubrum*
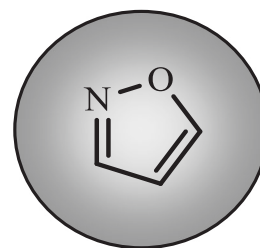TRPM   Transient receptor potential melastatin
TRPV   Transient receptor potential vanilloid

Fig. 1 Structure of isoxazole

Several marketed drugs with isoxazole nucleus belong to different categories with diverse therapeutic activities that have resulted in the development of a plethora of method for the synthesis of this valuable fragment. Such drugs are listed in Table 1. Inspired by these observations, this review summarizes current propensity in the isoxazole synthetic chemistry and divulges the utility of this potent nucleus as a rich source of new compounds having promising biological activities. Although several reviews have been published earlier on isoxazole (Manna et al. 2014; Hu and Szostak 2015; Chikkula and Raja 2017; Sysak and Obmińska-Mrukowicz 2017), the focus was either synthetic routes or chemical reactions of the nucleus or the several biological activities of the isoxazole derivatives. Our effort is an exhaustive and systematic compilation of synthetic, as well as therapeutic voyage of isoxazole and its derivatives till now.

Synthetic methods
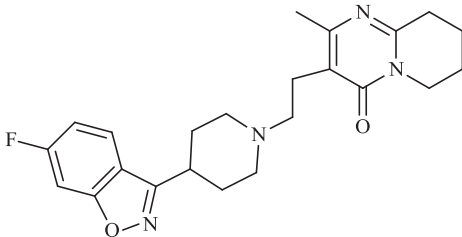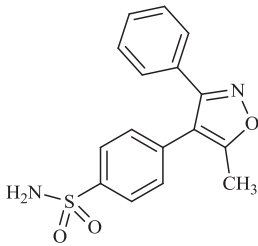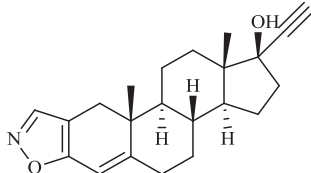
Literature survey revealed that several substituted isoxazoles had been prepared from numerous synthetic routes. The first contribution to the chemistry of isoxazoles was made by Claisen in 1903, when he synthesized the first compound of series, isoxazole, by oximation of propargylaldehyde acetal (Claisen 1903).

A regioselective, experimentally convenient one-pot copper(I)-catalyzed procedure was developed for the rapid synthesis of 3,5-disubstituted isoxazoles (Route a, Fig. 2) by reacting in situ generated nitrile oxides and terminal acetylenes (Hansen et al. 2005). Reddy et al. synthesized 3,5-disubstituted isoxazoles (Route b, Fig. 2) using *p*-tosylalcohol(TSA)-catalyzed reaction between propargylic alcohols and N-protected hydroxylamines followed by tetrabutylammonium fluoride (TBAF) mediated detosylation 5-*endo-dig* cyclization (Raji Reddy et al. 2012). Perez et al. reported an experimentally and environmentally benign one-pot three component process for the regioselective synthesis of 3,5-disubstituted isoxazoles (Route c, Fig. 2) from aldehydes and alkynes using choline chloride (ChCl): urea as a biorenewable deep eutectic solvent (DES). DES are an environmentally benign alternative to hazardous

Introduction

Heterocyclic compounds have attracted considerable attention as they act as a bridge between chemical and life sciences. A significant amount of contemporary investigation is currently pursued on these compounds worldwide. The chemistry of isoxazoles (Fig. 1) has been an interesting field of study for decades because of their prominent potential as analgesic (Karthikeyan et al. 2009), anti-inflammatory (Rajanarendar et al. 2015; Banoglu et al. 2016), anticancer (Kumbhare et al. 2012; Tzanetou et al. 2014), antimicrobial (Siddiqui et al. 2013; Basha et al. 2015), antiviral (Lee et al. 2009), anticonvulsant (Frølund et al. 2007), antidepressant (Yu et al. 2012; Zhang et al. 2016) and immunosuppressant (Ye et al. 2015). The literature survey revealed that the substitution of various groups on the isoxazole ring imparts different activity.

Table 1 Marketed drugs containing isoxazole nucleus
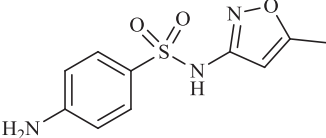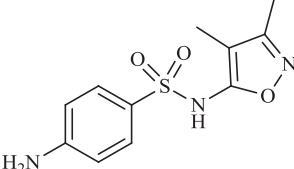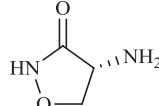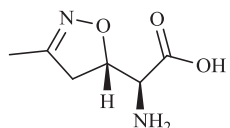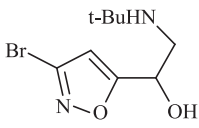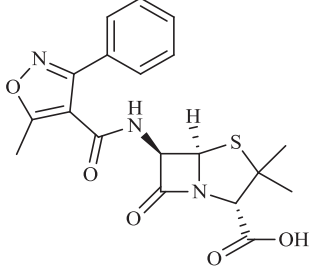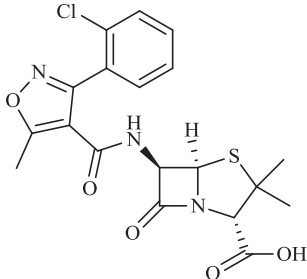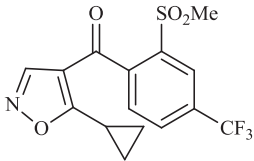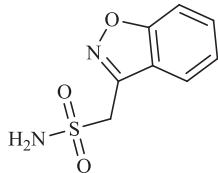
S. No.	Name of the drug	Structure	Pharmacological class
1	Sulfamethoxazole		Antibacterial (Majewsky et al. 2014)
2	Sulfisoxazole		Antibacterial (Genc et al. 2008)
3	Acetyl sulfisoxazole		Antibacterial (Cronin et al. 2002)
4	Cycloserine		Antitubercular, Antileprotic (Desjardins et al. 2016)
5	Acivicin		Antitumour, Antileishmania (Conti et al. 2003)
6	Broxaterol		Bronchodilatory agent (Giustina et al. 1995)
7	Oxacillin		Antibacterial (Lainson et al. 2017)

Table 1 (continued)

S. No.	Name of the drug	Structure	Pharmacological class
8	Cloxacillin		Antibacterial (Mani and Iyyadurai 2017)
9	Isoxaflutole		Pesticide (Zhao et al. 2017a)
10	Zonisamide		Anticonvulsant (Buoli et al. 2017), Antiobesity (Shin et al. 2014)
11	Risperidone		Antpsychotic (Schoretsanitis et al. 2017)
12	Valdecoxib		COX-2 inhibitor (Bartzatt 2014)
13	Danazol		Androgenic (McKinney et al. 2013)

Table 1 (continued)

S. No.	Name of the drug	Structure	Pharmacological class
14	Leflunomide		Antirheumatic (Golicki et al. 2012)
15	Isocarboxazid		Antidepressant (Shader and Greenblatt 1999)
16	Drazoxolon		Antifungal (Lehtonen et al. 1972)

(organic) solvents that can be recycled (Pérez and Ramón 2015). Jadhav et al. synthesized highly pure 3,5-dis-ubstituted isoxazoles (Route d, Fig. 2) by converting aldoximes to nitrile oxides in the presence of Hydroxy (tosyloxy) iodobenzene (HTIB) and then reacting them with alkynes. The reagent HTIB is stable and can be handled without special care (Jadhav et al. 2013).

A highly regioselective method for the one-pot prepara-tion of 3,5-disubstituted isoxazoles (Route e, Fig. 2) involves the reaction of terminal alkynes with *n*-BuLi and then aldehydes followed by the treatment with molecular iodine and subsequently with hydroxylamine (Harigae et al. 2014). Huang et al. (2014) reported an environmentally benign procedure for the synthesis of 3-alkyl-5-aryl iso-xazoles (Route f, Fig. 2) under ultrasound radiation without using any catalyst. This method has advantages of easier work-up, mild reaction condition, high yields and shorter reaction time. Trogu et al. (2012) discovered a faster and efficient method for preparation of 3,5-disubstituted iso-xazoles (Route g, Fig. 2) by base catalyzed condensation reactions of nitroacetic esters with dipolarophiles in the presence of water instead of chloroform.

Mohammed and coworkers synthesized isoxazoles (Route h, Fig. 2) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a reagent which promotes the 1,3-dipolar addition

of nitrile oxides with alkynes without the use of metal (Mohammed et al. 2015). Kesornpun et al. performed cycloaddition of nitrile oxides with alkynes in aqueous solutions under acidic conditions rather than under the conventional basic conditions (Kesornpun et al. 2016). 5-arylisoxazole derivatives (Route i, Fig. 2) can be synthe-sized using an environmentally benign procedure via the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-ones with hydroxylamine hydrochloride in the aqueous medium without using any catalyst (Dou et al. 2013). Valizadeh et al. introduced an environment-friendly synthesis for 3,5-disubstituted isoxazoles (Route j, Fig. 2) using ionic liquids (IL). A typical reaction of β-diketone with hydroxylamine was carried out in the IL, butylmethylimidazolium salts ([BMIM]X) to form isoxazoles in excellent yields (Valiza-deh et al. 2009). The IL was recovered and recycled successfully.

Various methods have been reported to prepare iso-xazoles with a variety of substituents at 3, 4, and 5 posi-tions. Denmark and Kallemeyn (2005) first synthesized isoxazolylsilanols by [3+2] cycloaddition reaction between alkynyldimethylsilyl ethers and aryl and alkyl nitrile oxides (Route a, Fig. 3). The cross-coupling reaction of these heterocyclic silanols with a variety of aryl iodides leads to the formation of a variety of 3,4,5-trisubstituted isoxazoles.

Fig. 2 Routes for the synthesis of 3,5-disubstituted isoxazoles
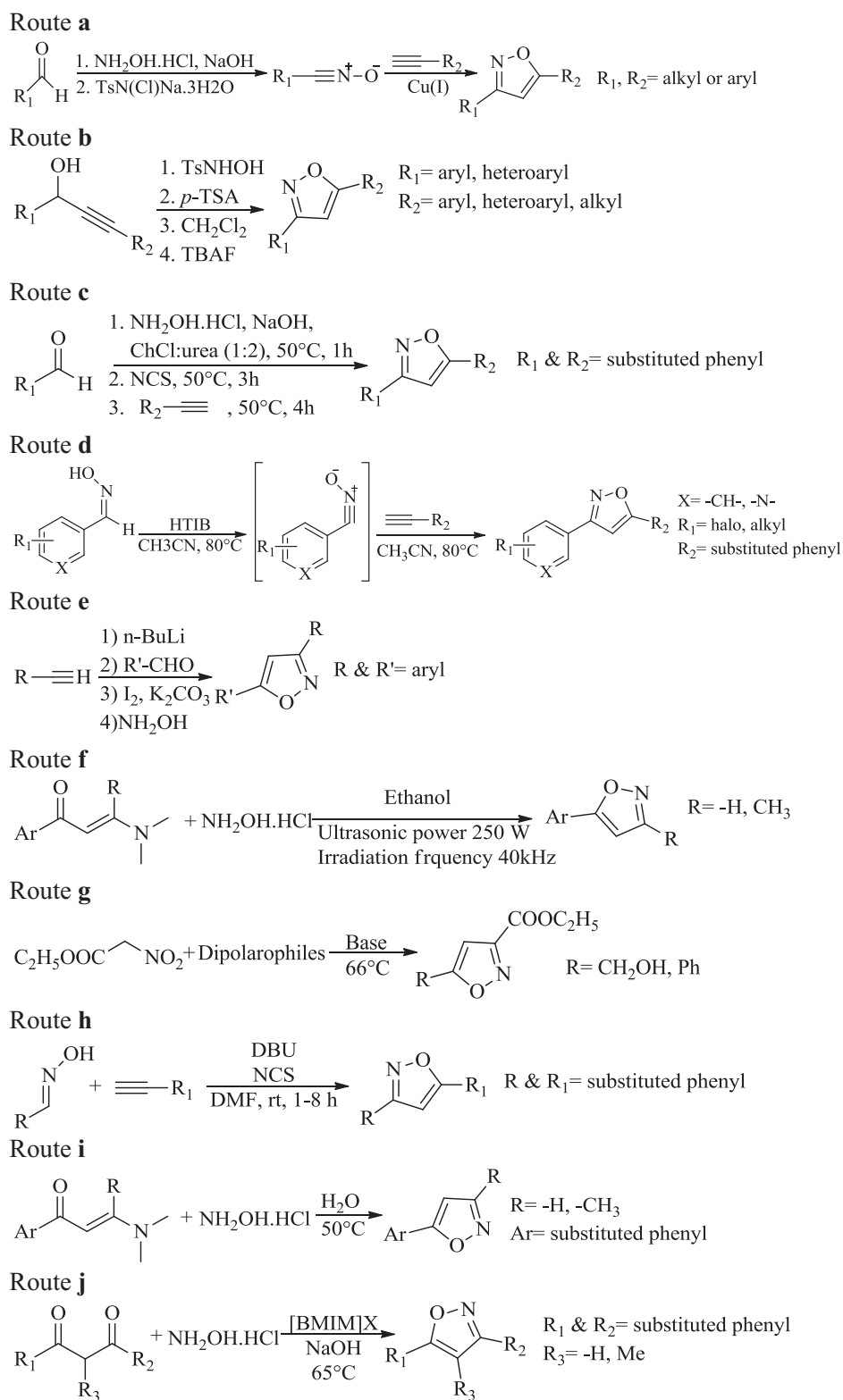
Gayon et al. (2011) synthesized trisubstituted isoxazoles using an uninterrupted four-step sequence method from readily available propargylic alcohols using sequentially iron and palladium catalyzed systems (Route b, Fig. 3).

The overall yields of this method were high, and it emerged as a time-saving procedure.

Recently, Li et al. (2017) used syringe pump infusion for the synthesis of polysubstituted isoxazoles (Route c, Fig. 3)

Fig. 3 Routes for the synthesis of 3,4,5-trisubstituted isoxazoles

Route **a**

R_1= Et, Ph
R_2= Me, Ph
R_3= NO$_2$, CH$_3$, OCH$_3$

Route **b**

R= alkyl

Route **c**

R_1= substituted phenyl
R_2 & R_3= -H, -COOMe

Route **d**

R= alkyl, aryl
Ar= substituted phenyl

Route **e**

R_1= alkyl, aryl, heteroaryl
R_2= SiMe$_3$, n-Bu
R_3= substituted phenyl

Route **f**

R_1= alkyl, aryl
R_2, R_3= H, Ph, CH$_2$OH
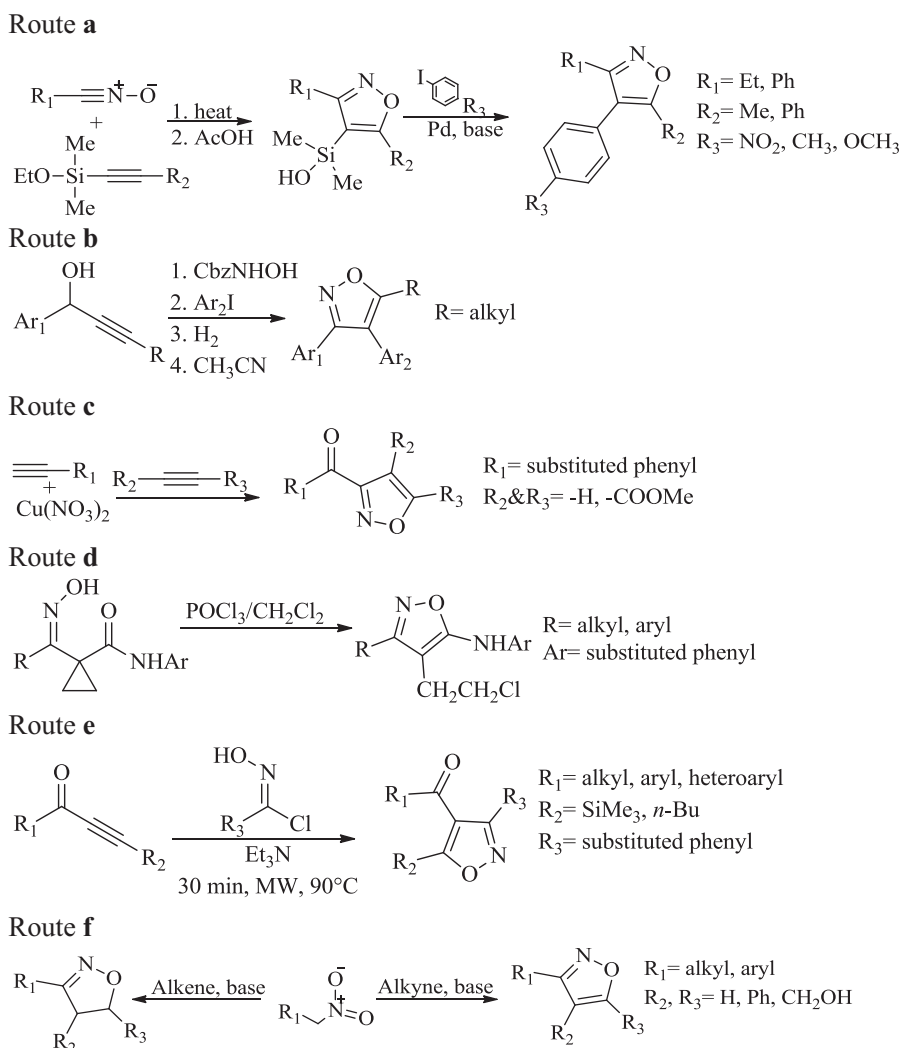
using a copper nitrate mediated synthesis from two different alkynes with high chemo-and regioselectivity. Substituted isoxazoles (Route d, Fig. 3) can be obtained from the cyclopropyl oximes (Wang et al. 2008) via ring-opening and intramolecular nucleophilic vinylic substitution reaction in the presence of POCl$_3$/CH$_2$Cl$_2$. Willy et al. (2008) synthesized 3,4,5-substituted isoxazoles (Route e, Fig. 3) by cycloaddition reaction between in situ generated nitrile oxide and alkynones in the presence of triethylamine using dielectric heating for 30 min. The primary activated nitro compounds condensed with alkenes to give isoxazolines and with alkynes to give isoxazoles (Route f, Fig. 3) in chloroform in the presence of 1,4-diazabicyclo[2.2.2]octane or other suitable N-bases via 1,3-dipolar cycloaddition (Machetti et al. 2007).

Different methods have been reported for the synthesis of aminoisoxazoles. Treatment of β-ketonitriles with hydroxylamine in aqueous ethanol (Route a, Fig. 4) gives 3-aminoisoxazoles (Elnagdi et al. 1975). One-pot three-component coupling of β-oxo dithioesters, amines and hydroxylamine in ethanol at reflux affords 5-substituted 3-aminoisoxazoles (Route b, Fig. 4) via an *in situ* generated β-oxo thioamide intermediate (Samai et al. 2013). 4-aminoalkylisoxazol-3-ones can be obtained from 3-allyllactams (bielectrophiles) in high yields (Nenajdenko et al. 2005). During the course of the reaction, closure of one heterocycle is accompanied by the opening of the other (Route c, Fig. 4).

3-aminocrotononitrile reacts with hydroxylamine hydrochloride (Route d, Fig. 4) to give 5-amino-3-methylisoxazole (Abushanab et al.. 1973). The [2+3] cycloaddition reaction of nitrile oxides with captodative olefins or methyl crotonate derivatives is regioselective (Route e, Fig. 4) and leads to the formation of the 5-substituted amino-isoxazole or the 4-substituted methoxycarbonyl-isoxazole derivatives, respectively (Lasri et al. 2008). The [4+1] cycloaddition reaction of isocyanides with α-haloketone oxime (Route f, Fig. 4) in the presence of

Fig. 4 Routes for the synthesis of aminoisoxazoles
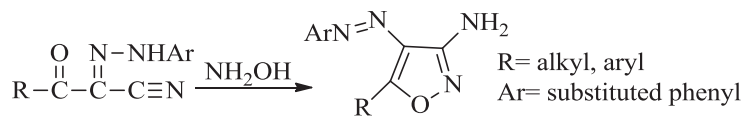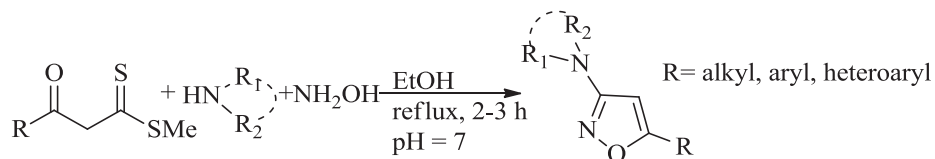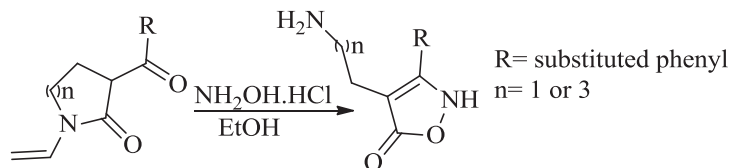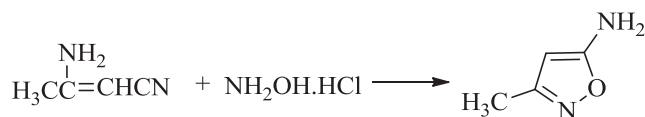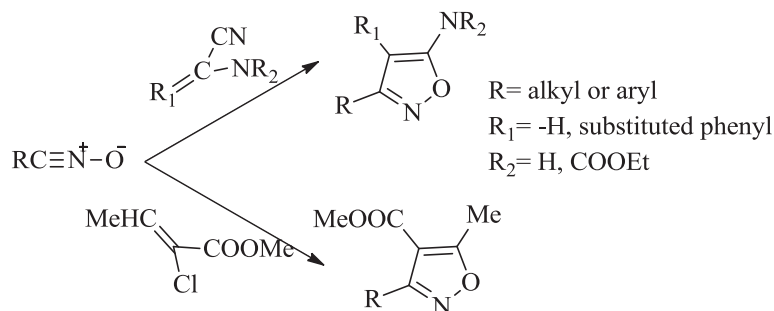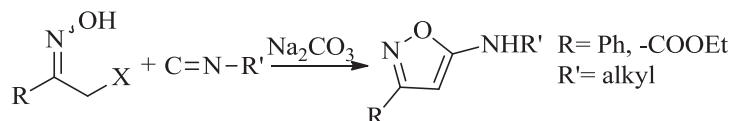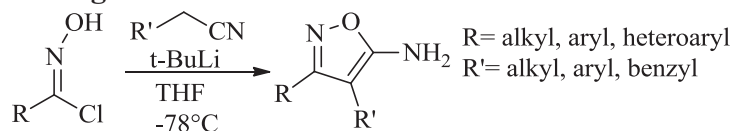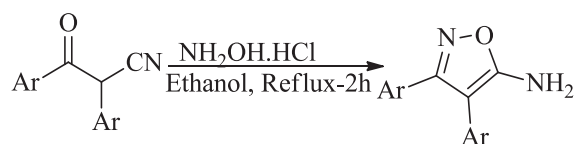
sodium carbonate yields 5-substituted aminoisoxazoles (Buron et al. 1997). While treatment of α-chloro oximes with lithiated nitriles, produced a variety of

5-aminoisoxazoles (Route g, Fig. 4) with alkyl functionality at 4-position (Bourbeau and Rider 2006). Liu et al. (2009) prepared 5-aminoisoxazoles (Route h, Fig. 4) by

Fig. 5 Routes for the synthesis of miscellaneous isoxazoles
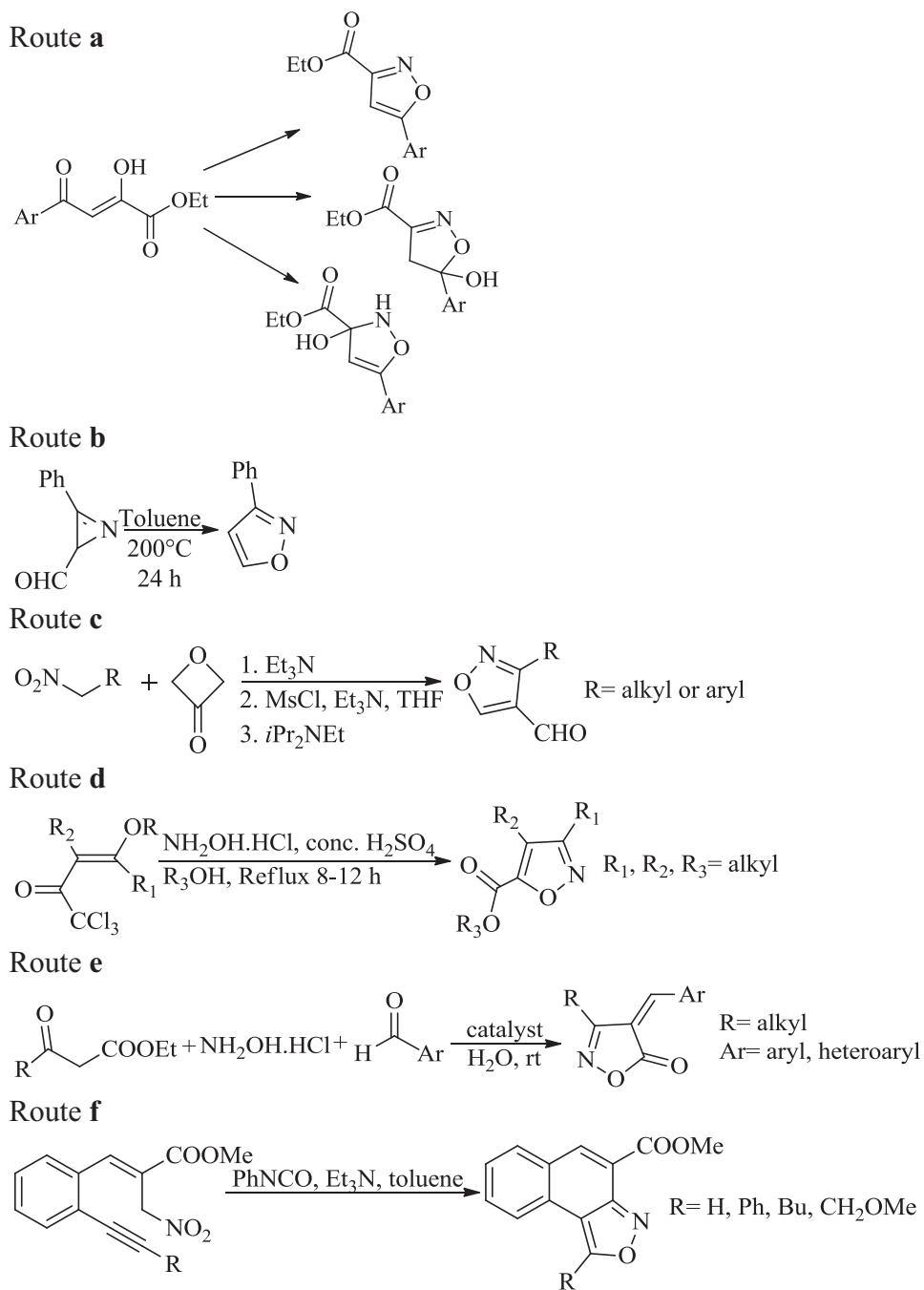
condensation of α-cyanoketones with hydroxylamine hydrochloride in refluxing alcohol.

Aryl 1,3-diketoesters reacts hydroxylamine hydrochloride under different pH conditions. Acid conditions gave 3,5-isoxazole esters (Route a, Fig. 5) principally whereas reactions under neutral and basic conditions led to different 4,5 and 2,3-dihydro-hydroxy-isoxazoles, respectively (Andrzejak et al. 2010). Heating of 2-formyl azirines for 24 h in toluene at 200°C (Route b, Fig. 5) affords isoxazole (Brahma and Ray 2008). 3-substituted isoxazoles-4-

carbaldehyde (Route c, Fig. 5) can be prepared by condensation reaction of nitroalkanes with 3-oxetanone (Burkhard et al. 2011). Martins et al. (2000) reported the synthesis of 5-carboxyisoxazoles (Route d, Fig. 5) from the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones with hydroxylamine in a hydrochloric acid or sulphuric acid medium.

4*H*-isoxazol-5-ones were synthesized by one-pot three-component condensation of aryl aldehydes, hydroxylamine hydrochloride and ketoesters using potassium phthalimide

Fig. 6 Routes for the synthesis of miscellaneous isoxazoles
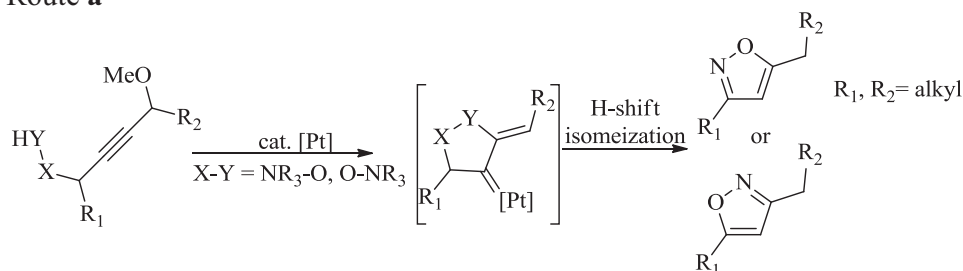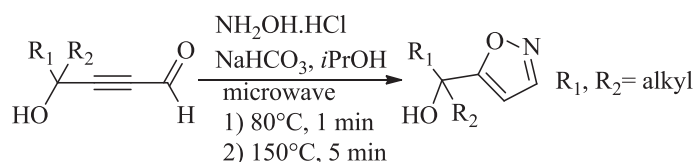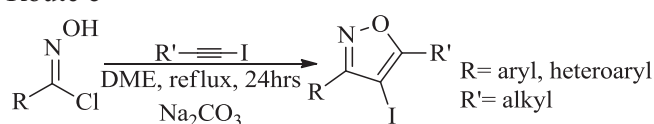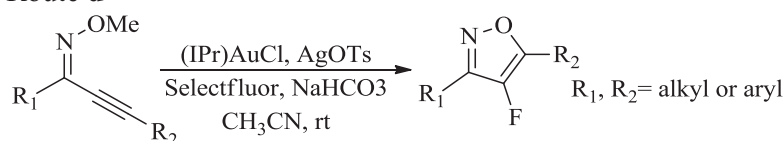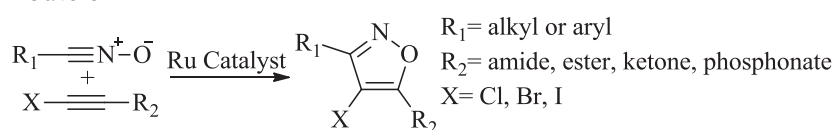
(Kiyani and Ghorbani 2013d), sodium ascorbate (Kiyani 2013), sodium tetraborate (Kiyani and Ghorbani 2013b), sodium azide (Kiyani and Ghorbani 2013c), sodium citrate (Kiyani and Ghorbani 2013a), sodium saccharin (Kiyani and Ghorbani 2013e), N-bromosuccinimide (Kiyani et al. 2015) or boric acid (Kiyani and Ghorbani 2015) as a catalyst in aqueous medium at room temperature (Route e, Fig. 5). Later Chavan et al. (2015) synthesized 4H-isoxazol-5-ones efficiently by one-pot uncatalyzed reaction of hydroxylamine hydrochloride, ketoesters and aromatic aldehydes substituted with electron donating group in the aqueous medium. Ji et al. (2006) synthesized 4-carbomethoxy-ynaphtho[2,1-c]isoxazoles (Route f, Fig. 5) from methyl 3-(alkynylphenyl)-2-propenoates by the intramolecular nitrile oxide cycloaddition.

Allegretti and Ferreira (2013) reported cyclization of propargylic N-hydroxycarbamates and N-alkoxycarbonyl amino ethers (Route a, Fig. 6) via Pt-carbene intermediate to differentially substituted regioisomeric isoxazoles. Recently, Bulanov et al. (2017) reported an efficient,

catalyst-free and microwave assisted one pot method for synthesis of 5-substituted isoxazoles (Route b, Fig. 6) from α-acetylenic γ-hydroxyaldehydes and hydroxylamine. Crossley and Browne (2010) synthesized a series of iodoisoxazoles (Route c, Fig. 6) by reacting hydroximinoyl chlorides and iodinated terminal alkynes. Jeong et al. (2014) synthesized a series of fluoroisoxazoles (Route d, Fig. 6) using one-pot gold-catalyzed tandem cyclization−fluorination of (Z)-2-alkynone O-methyl oxime under mild conditions (room temperature). Further, Oakdale et al. (2014) synthesized 4-haloisoxazoles (Route e, Fig. 6) using ruthenium-catalyzed cycloaddition of nitrile oxides with electronically deficient 1-haloalkynes.

Biological activities

Owing to the diverse and potential pharmacological activities of the isoxazole ring, many researchers across the globe are engaged in the development of pharmacologically

active agents bearing it. The following discussions illustrate the pharmacological applications of isoxazole against various biological properties.

Analgesic and anti-inflammatory activity

Rajanarendar et al. (2015) synthesized some 6-methyl isoxazolo[5,4-*d*]isoxazol-3-yl aryl methanones, assessed them for molecular properties prediction, drug-likeness, lipophilicity and solubility parameters, evaluated for in vitro COX inhibitory activity and screened for anti-inflammatory activity using carrageenan induced paw edema method. The compounds with chloro or bromo substitutions on phenyl ring (**1**; Fig. 7) exhibited significant anti-inflammatory activity and were more selective towards COX-2 enzyme. Habeeb et al. (2001) reported the synthesis of 4,5-diphenyl-4-isoxazolines possessing a variety of substituents at the para position of one of the phenyl ring and evaluated for analgesic and selective COX-2 anti-inflammatory activity. The compounds having C-3 Me substituent on central isoxazoline ring were potent analgesics, as well as selective towards COX-2. 4,5-diphenyl-5-(4-methylsulfonylphenyl)-4-phenyl-4-isoxazoline and screened for anti-inflammatory activity. Among these, the compound **2** (Fig. 7) having a sulfonylmethyl group at the para position of phenyl ring was most potent analgesic, as well as anti-inflammatory agent. Molecular modeling studies on **2** showed that the S atom of sulfonylmethyl and the C-3 Me group was crucial for selective inhibition of COX-2. Perrone et al. (2016) synthesized a new series of isoxazole and evaluated them for their COX inhibitory activity and selectivity. Compound **3** (Fig. 7) was found to be a sub-micromolar selective COX-2 inhibitor (IC$_{50}$ 0.95 μM).

Some indolyl-isoxazoles (**4**; Fig. 7) were synthesized by Panda et al. and evaluated for acute anti-inflammatory activity using carrageenan-induced rat paw edema method. All the compounds exhibited good anti-inflammatory activity ranging from 36.6 to 73.7% reduction in edema (Panda et al. 2009). Another series of indole derivatives bearing isoxazoline moiety were synthesized by Amir et al. (2010) and tested in vivo for their anti-inflammatory activity by carrageenan-induced rat paw edema method. From these studies compound **5** (Fig. 7) showed maximum anti-inflammatory activity along with a maximum reduction in ulcerogenic activity and lipid peroxidation. Karthikeyan et al. (2009) reported the synthesis of a series of pyrazolyl isoxazolines **6** and isoxazoles **7** (Fig. 7) using 1,3-dipolar cycloaddition of pyrazole derived nitrile oxides with various dipolarophiles. The synthesized compounds were evaluated for antinociceptive activity. All the compounds displayed efficacy comparable to standard drugs pentazocine and aspirin.

Chemical-cooling agents like menthol induce analgesia by activating TRPM8 channels that act as a Ca^{2+}-permeable ligand-gated cation channel. Some aminoisoxazole-based derivatives synthesized by Ostacolo et al. (2013) were able to modulate TRPM8 that can be used for cold-evoked analgesia. The ability of the compounds to act as TRPM8 agonists was studied using [Ca^{2+}]-imaging experiments in sensory neurons in vitro, and an in vivo model of cold allodynia. Some of the compounds were up to 200-fold more potent than menthol, but none of them showed improved efficacy. The compound **8** (Fig. 7) was most promising. TRPV1 channels are Ca^{2+}-permeable non-selective cation channel expressed in primary afferent neurons and are the integrator of nociceptive responses to both chemical and noxious stimuli. After the HTS, Palin et al. (2011) synthesized an isoxazole-3-carboxamide series and evaluated them for their ability to modulate TRPV1 channel. Substitution of isoxazole-3-carboxamide with 1*S*, 3*R*-3-aminocyclohexanol motif (compounds **9** and **10**; Fig. 7) aided both potency and solubility. These compounds were further progressed to animal studies, where both the compounds attenuated the acute inflammatory response in the rat complete Freund's adjuvant assay.

A series of 4,5-diaryloisoxazol-3-carboxylic acids was synthesized by Banoglu et al. (2016) as leukotriene biosynthesis inhibitors targeting FLAP. Leukotrienes have important roles in various inflammatory diseases. In the very first step of leukotriene biosynthesis, there is an involvement of FLAP. Compounds **11a** and **11b** (Fig. 7) emerged as potent anti-inflammatory agents possessing potent inhibitory activity against cellular 5-Lipoxygenase product synthesis with IC$_{50}$ of 0.24 μM each. Silva et al. (2002) synthesized isoxazole derivatives as nAChR ligands for the development of analgesics. nAChR has gained much attention due to beneficial effects of nicotine in CNS disorders such as Alzheimer's disease, Parkinson's disease, and pain reflexes. Compound **12** (Fig. 7) displayed the best analgesic profile in the series. Peifer et al. (2009) synthesized 3,4-diaryl isoxazoles as a dual inhibitor of p38α MAP kinase and CK1δ. Compounds **13** and **14** (Fig. 7) were found to be highly potent dual inhibitors of p38α and CK1δ. p38α MAP kinase plays a major role in signal transduction of severe inflammatory diseases like rheumatoid arthritis, asthma and autoimmune disorders (Peifer et al. 2006). Laufer et al. (2006) synthesized 3,4 and 4,5-disubstituted and 3,4,5-trisubstituted isoxazoles which were tested in an in vitro ELISA of isolated p38 MAP kinase and for inhibitory potency against cytP450 to develop agents for the treatment of rheumatoid and inflammatory diseases. The pyridinyl isoxazole (**15**; Fig. 7) displayed significant suppression of cytokine release, low affinity towards cytP450 and potent inhibitory activity towards isolated p38 MAP kinase.
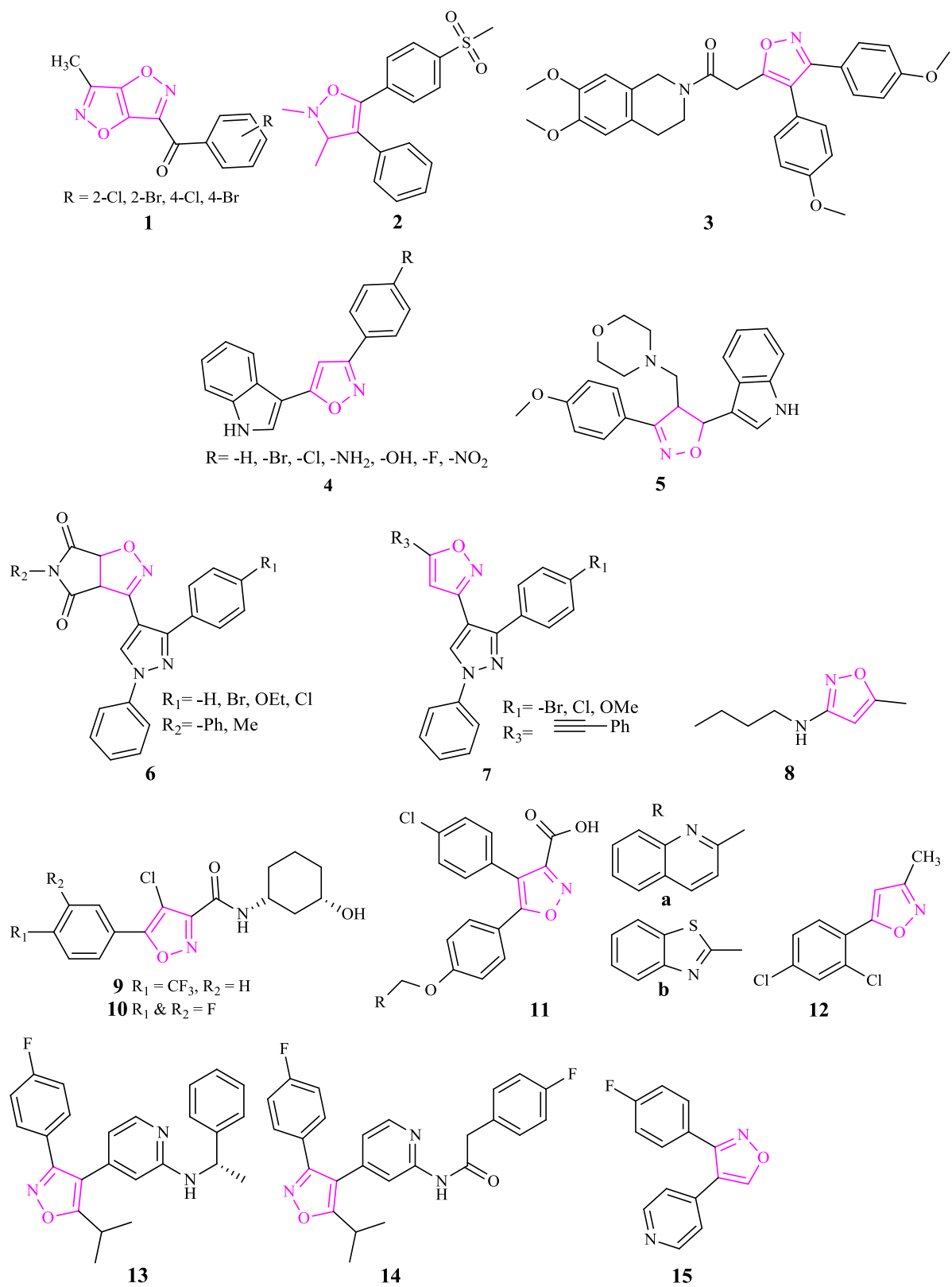
Fig. 7 Isoxazole derivativess showing analgesic and anti-inflammatory activity (**1**–**15**)
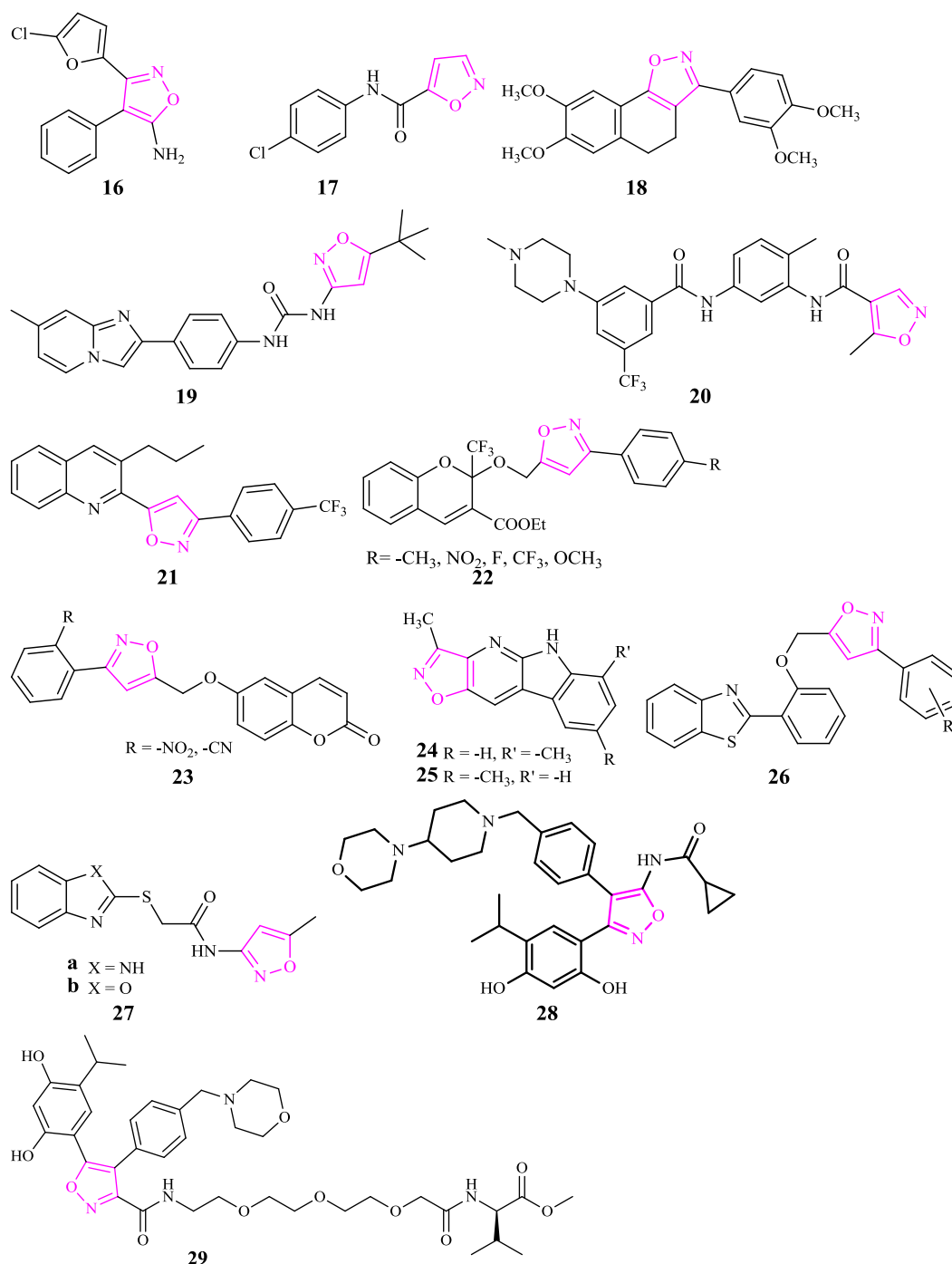
Fig. 8 Isoxazole derivatives showing anticancer activity (16–29)

Antitumor/anticancer activity

Vitale et al. (2014) designed and synthesized new isoxazoles taking [3-(5-chlorofuran-2-yl)-5-methyl-4-phenylisoxazole], a highly selective COX-1 inhibitor (Vitale et al. 2013) as a lead. COX-1 inhibition is considered as a promising therapeutic strategy for cancer and neuro-inflammation-derived neurodegenerative diseases. All the compounds were evaluated for their in vitro COX inhibitory activity and selectivity. The substitution of methyl in the lead compound with an amino group (16; Fig. 8) improved the COX-1 selectivity and inhibitory activity. Instead low or no activity was observed for its N,N-dialkyl and N,N-diacetyl derivatives. The inhibitory activity of compound 16 (Fig. 8) was also assessed in ovarian cancer cell line (OVCAR-3) where it was found to be 20-fold more potent than the lead compound.

Shaw et al. (2012) synthesized N-phenyl-5-carboxamidyl isoxazoles and screened for their cytotoxic activity against colon 38 and CT-26 mouse colon tumor cells. The most active and solid-tumor compound **17** (Fig. 8) (IC$_{50}$ 2.5 μg/mL) significantly downregulated the expression of phosphorylated-STAT3, a novel target for chemotherapeutic drugs, in both human and mouse colon cancer cells. Tzanetou et al. (2014) synthesized tetralone-isoxazole fused compounds and evaluated in four different cell lines: two endothelial cell lines (HMEC-1 and MBEC) and two tumor cell lines [human cervical carcinoma (HeLa) and human breast carcinoma (MCF-7) cells. Compound **18** (Fig. 8) exhibited promising cytostatic activity, demethylation of which led to 10-fold less active compound.

Over-expression of FLT3 plays a critical role in development and progress of acute myeloid leukemia. Xu et al. (2015) designed and synthesized a series of novel N-(5-(*tert*-butyl)isoxazol-3-yl)-N′-phenylurea derivatives as FLT 3 inhibitors. Among the synthesized compounds, compound **19** (Fig. 8) inhibited the phosphorylation of FLT3 and led to complete tumor regression in the MV4-11 xenograft model. Compound **19** (Fig. 8) also displayed acceptable aqueous solubility, desirable pharmacokinetic properties and high cytotoxic selectivity against MV4-11 cells. SAR studies revealed that an electron-rich fused ring (R) at the phenyl was beneficial for the antiproliferative activity. Im et al. (2015) synthesized a series of 4-arylamido 3-methylisoxazoles and evaluated them for antiproliferative activities against the A375P melanoma and U937 hematopoietic cell lines. Most of the compounds displayed selective antiproliferative activity toward the U937 cell line, and the activities were better than the reference drug Sorafenib while weak cytotoxic activities against human normal cell line and A375P. The most potent inhibitor **20** (Fig. 8) was found to be a potent inhibitor of FMS kinase too with an IC$_{50}$ of 9.95 nM. The FMS kinase inhibitors have great potential in the treatment of bone osteolysis and inflammation, as well as cancers promoted by macrophages.

Sambasiva Rao et al. (2014) synthesized 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives and screened against four human cancer cell lines (A549, COLO 205, MDA-MB 231 and PC-3). Compound **21**(Fig. 8) showed potent cytotoxicity against all the tested cell lines at IC$_{50}$ < 12 μM. The SAR revealed that fluorine or trifluoromethyl group at the fourth position of phenyl in isoxazole ring promotes the cytotoxicity. Ratnakar Reddy et al. (2014) prepared isoxazole functionalized chromene derivatives (**22**; Fig. 8) and screened against four human cancer cell lines namely A549-Lung Cancer (CCL-185), MCF7-Breast cancer (HTB-22), DU145-Prostate cancer (HTB-81), HeLa-Cervical cancer (CCL-2) using 5-Fluorouracil as a positive

control by MTT assay. All the compounds displayed poor to moderate activity.

Shakeel-u-Rehman et al. (2014) linked 6-hydroxycoumarins to isoxazole and screened for their cytotoxic activity against five different human cancer cell lines namely prostate (PC-3), colon (HCT-116 and Colo-205), leukemia (HL-60) and lung (A-549). The ortho substituted isoxazole derivatives of 6-hydroxy coumarin (**23**; Fig. 8) emerged as effective cytotoxic agents against PC-3 cancer cell line. Rajanarendar et al. (2015) synthesized a series of novel isoxazolo[5′,4′:5,6]pyrido[2,3-*b*]indoles and evaluated against three human cancer cell lines Hela, MCF-7 and NCI-H460 (lung cancer) according to MTT assay method using Cisplatin as a reference drug. Compounds **24** and **25** (Fig. 8) displayed potent anticancer activity comparable to reference drug towards all the tested cancer cell lines. Rest of the compounds exhibited moderate to good anticancer activity with low selectivity.

Isoxazoles linked 2-phenylbenzothiazole **26** (Fig. 8), synthesized by Kumbhare et al. (2012), displayed significant anticancer activity against MCF-7 cells (IC$_{50}$ 26–43 μM), A549 cells (human lung adenocarcinoma; IC$_{50}$ 11–24 μM) and Colo-205 cells (human colon cancer; IC$_{50}$ 11–21 μM) and possessed the ability to cause apoptosis. Özkay et al. (2013) synthesized some isoxazole-(benz)azole derivatives and evaluated them for cytotoxic effects on HT-29 (colon carcinoma) and C-6 (melanoma) cell lines using MTT assay. The compounds which displayed significant cytotoxicity were selected and then analyzed for their inhibitory activity on DNA synthesis of carcinogenic cells. The compounds **27a** and **27b** (Fig. 8) showed potent cytotoxic activity against both cancer cell lines and displayed significant inhibitory activity on DNA synthesis of carcinogenic cells.

Hsp90 is overexpressed in a number of human cancers that makes it a potential target for cancer treatment. Chen et al. (2014) synthesized a series of small molecules with 4,5-diarylisoxazole scaffold and evaluated them for Hsp90 inhibitory activity. In this series, compound **28** (Fig. 8) showed high affinity for Hsp90 and strongly inhibited it at both molecular and cellular level. Further in vivo studies showed that compound **28** (Fig. 8) strongly suppresses the tumor growth of human glioblastoma xenograft model U-87MG and displayed good results in pharmacokinetic and safety experiments. Another series of 4,5-diaryl isoxazoles was synthesized by Zhang et al. (2017) by incorporating diversified amino acid derivatives with various lengths to the 3-amido motif. These compounds were evaluated for Hsp90 inhibitory activity and antiproliferative activity against H3122 human lung cancer and BT-474 breast cancer cells. Compound **29** (Fig. 8) bearing a terminal valine methyl ester and an ethylene glycol-containing linear linker displayed high Hsp90 binding potency (14 nM), as well as

R1= -Ph, 2-Pyrazine
R2= -H, OH, OAc, OMe
30

31

32

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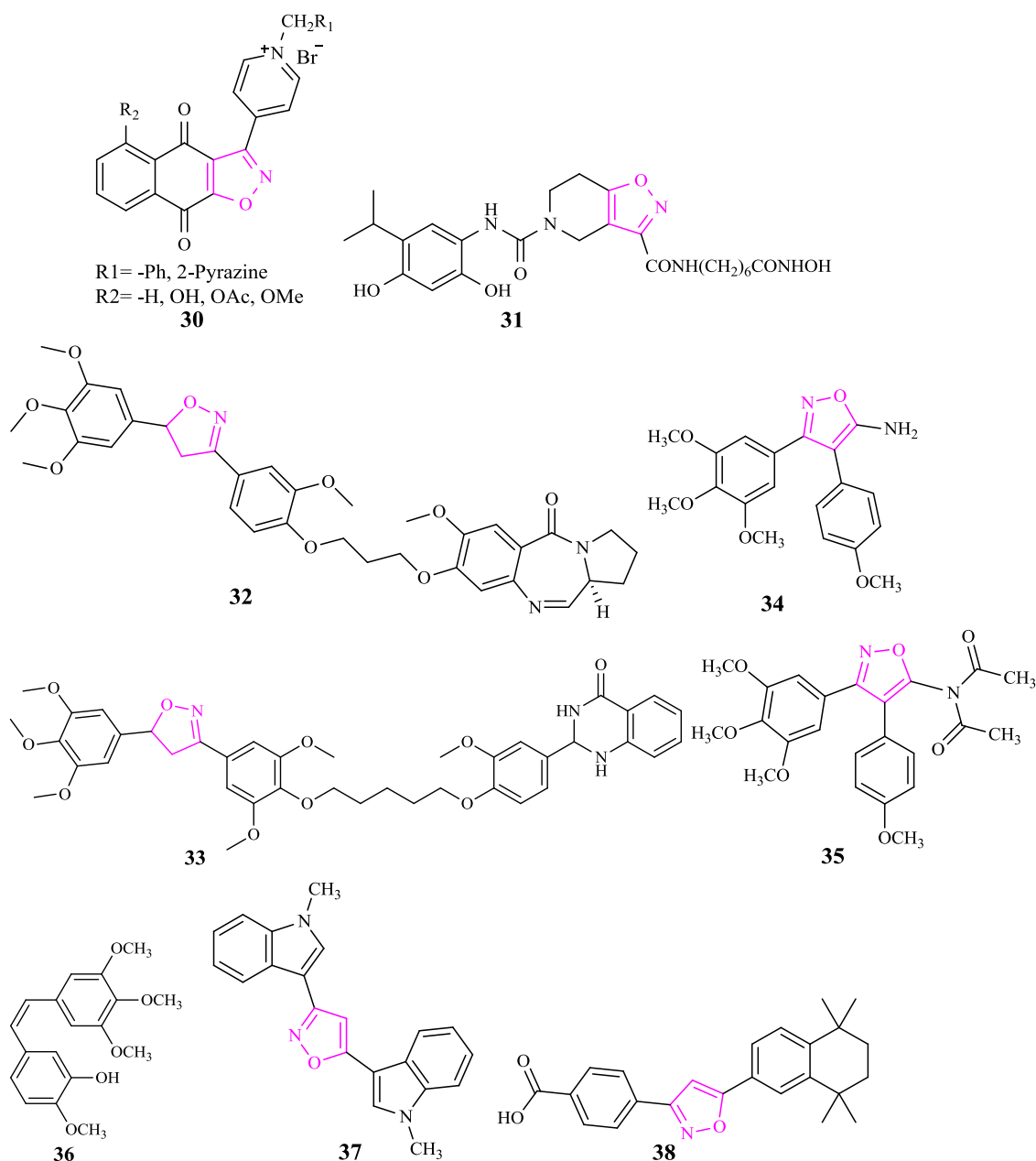
Fig. 9 Isoxazole derivatives showing anticancer activity (**30–38**)

antiproliferative activity against the tested cell lines. Bargiotti et al. (2012) synthesized isoxazolo(aza)naphthoquinones and evaluated them for cytotoxic Hsp90 inhibitory activity in a series of human tumor cell lines. Most of the compounds mainly 3-pyridyl derivatives (**30**; Fig. 9) displayed high affinity and potent antiproliferative activity.

Baruchello et al. (2014) reported Hsp90 and HDAC6 inhibitory activity of 4,5,6,7-tetrahydro-isoxazolo-[4,5-c] pyridine compounds and evaluated for antiproliferative activity. The N-5 substitution with a 2,4-resorcinol carboxamide appeared to be crucial for activity. Compound **31** (Fig. 9) with a long chain hydroxamic residue bound to C-3

amide portion inhibited both Hsp90 and HDAC6. Kamal et al. synthesized a series of 3,5-diaryl isoxazoline/isoxazole linked pyrrolo-benzodiazepine (Kamal et al. 2010) and 2,3-dihydroquinazolinones (Kamal et al. 2011) and evaluated for their anticancer activity. From the former series, compound **32** (Fig. 9) exhibited G0/G1 arrest, activation of caspase-3 and finally apoptotic cell death. Compound **33** (Fig. 9) from the latter series showed the disruption of microtubules, as well as fragmentation of nuclei and emerged as an efficient cyclin B1 inhibitor, as well as a CDK1 inhibitor and this hybrid compound was effective against 18 human cancer cell lines.

Liu et al. (2009) synthesized a series of *cis*-restricted 3,4-diaryl-5-aminoisoxazoles and evaluated against five human cancer cell lines (human myeloid leukemia cells K562, human esophageal carcinoma cells ECA-109, human non-small lung cancer cells A549, human hepatocellular carcinoma cells SMMC-7721, and human prostate carcinoma cells PC-3). The tested compounds displayed more potent cytotoxic activity against leukemia cells K562 than other cell lines. However, the compounds **34** (Fig. 9) and its *N,N*-diacetyl derivative (**35**; Fig. 9) exhibited potent in vitro cytotoxic activities with IC$_{50}$ values in the range of 0.04–12.00 µM against all tested cancer lines and inhibited tubulin polymerization similar to that of combretastatin A-4 (**36**; Fig. 9), a potent antitumor agent.

Diana et al. (2010) synthesized a series of novel 2,5-bis(3′-indolyl)furans and 3,5-bis(3′-indolyl)isoxazoles and evaluated their antiproliferative activity in vitro against diverse human tumor cell lines. Among the isoxazoles, compound **37** (Fig. 9) was found to be most active and showed high selectivity towards 29 cell lines. Simoni et al. (2001) synthesized retinoic acid receptor ligands with potent apoptotic activity. Retinoids play a major role in regulating the growth and differentiation of a wide variety of normal and malignant cell types. Compound **38** (Fig. 9) exhibited good affinity for the retinoid receptors. Moreover, its ability to act on K562 and HL60R cell lines suggested its important implications in the treatment of different leukemias.

SIRT1/SIRT2 inhibitors have been found to possess antitumor activity. Mahajan et al. (2014) synthesized pyrazolone and isoxazol-5-one cambinol analogs and reported their sirtuin inhibitory activity with in vitro and in vivo anti-lymphoma activity. Among them, the isoxazole derivatives have emerged as selective SIRT 2 inhibitor displaying >15.4-fold SIRT-2 selectivity. The SIRT-2 selective inhibitor **39** (Fig. 10) exhibited potent cytotoxicity in both lymphoma and epithelial cancer cell lines with IC$_{50}$ ranging from 3 to 7 µM.

Panathur et al. (2015) synthesized a new series of indole–isoxazolone hybrids bearing substituted amide, substituted [(1,2,3-triazol-4-yl)methoxy]methyl group or substituted benzylic ether at position-2 of the indole. The molecules were screened for anticancer activity against three human cancer cell lines (MDA-MB-231, MCF-7, and HT-29). Most of the trifluoromethyl substituted derivatives exhibited better growth inhibition activity than their methyl substituted analogs. The SIRT1 inhibition activity of two potent molecules (**40a** and **40b**; Fig. 10) was investigated, and the SIRT1 IC$_{50}$ values were 35.25 and 37.36 µM, respectively. 3-amino-benzo[*d*]isoxazole based compounds were synthesized by Jiang et al. (2015) and evaluated for their tyrosine kinase c-Met inhibitory activity. This tyrosine kinase c-Met is a receptor for hepatocyte growth factor. Abnormality in this pathway leads to tumor growth, angiogenesis, and metastasis. Compound **41a** and **41b**

(Fig. 10) displayed most potent c-Met inhibitory activity both at enzymatic (IC$_{50}$ 1.8 nM) and cellular (IC$_{50}$ 0.18 nM) levels with high antiproliferative efficacy against EBC-1 (human lung squamous carcinoma) cell line.

Chouaïb et al. (2016) synthesized 3,5-disubstituted isoxazoles from natural maslinic acid and oleanolic acids and evaluated them for anti-inflammatory and antiproliferative activity against murine mammary carcinoma cell line EMT-6 and human colorectal adenocarcinoma cell line SW480. Among all the derivatives, the compound **42** (Fig. 10) bearing a furfuryl ring at its isoxazole moiety was found to possess promoting anti-inflammatory and anticancer effects. Najafi et al. (2015) prepared triazole-isoxazole derivative and evaluated for their cytotoxic activity against two human breast cancer cell lines MCF-7 and T-47D. Compounds **43a** and **43b** (Fig. 10) were found to be effective in vitro anticancer agents. However, no compound showed significant activity against tested cancer cell lines.

Pedada et al. (2016) synthesized a series of indole-containing isoxazoles and evaluated them for sPLA$_2$ inhibitory activity. sPLA$_2$ inhibitors are used for the preventive and therapeutic treatment of inflammatory diseases including cancer. All the compounds showed significant in vitro and in vivo sPLA$_2$ inhibitory activity. It was observed that isoxazoles with an electron withdrawing group like–F, CF$_3$ on phenyl ring displayed excellent sPLA$_2$ inhibitory activities. In particular, compound **44** (Fig. 10) showed potent sPLA$_2$ inhibitory activity comparable to positive control ursolic acid and exhibited in vitro antiproliferative activity against MCF-7 breast and DU145 prostate cancer cell lines. Yang et al. (2017) synthesized pyridinyl-4,5-2*H*-isoxazole derivatives and evaluated them for their in vitro inhibitory activity against MCF-7 cell line. Only the compounds with hydrophobic groups on phenyl displayed potent biological activities. Compounds **45a** and **45b** (Fig. 10) displayed highest anti-tumor activity and were found to possess potent antiproliferative activity against Human hepatoma cell line (HepG2) and cervical cancer cell line (HeLa) also.

Kalirajan et al. (2012) synthesized isoxazole substituted 9-anilinoacridine derivatives and evaluated them for in vitro antioxidant, as well as cytotoxic activity against Hep2 cell line. All the compounds possessed significant antioxidant activity and compound **46** (Fig. 10) displayed potent anticancer activity. Md Tohid et al. (2012) synthesized diarylisoxazoles containing an indole group either at 3-position or 5-position of isoxazole core and evaluated for their pro-apoptotic antitumor activity. The indol-5-yl substituted compounds (**47**; Fig. 10) were the most active, as well as selective when tested for their in vitro growth inhibitory activity against Colo320 (colon) and Calu-3 (lung) human cancer cell lines. These compounds had little or no effect on normal cell line viability suggesting their selective pro-apoptotic antitumor effects.
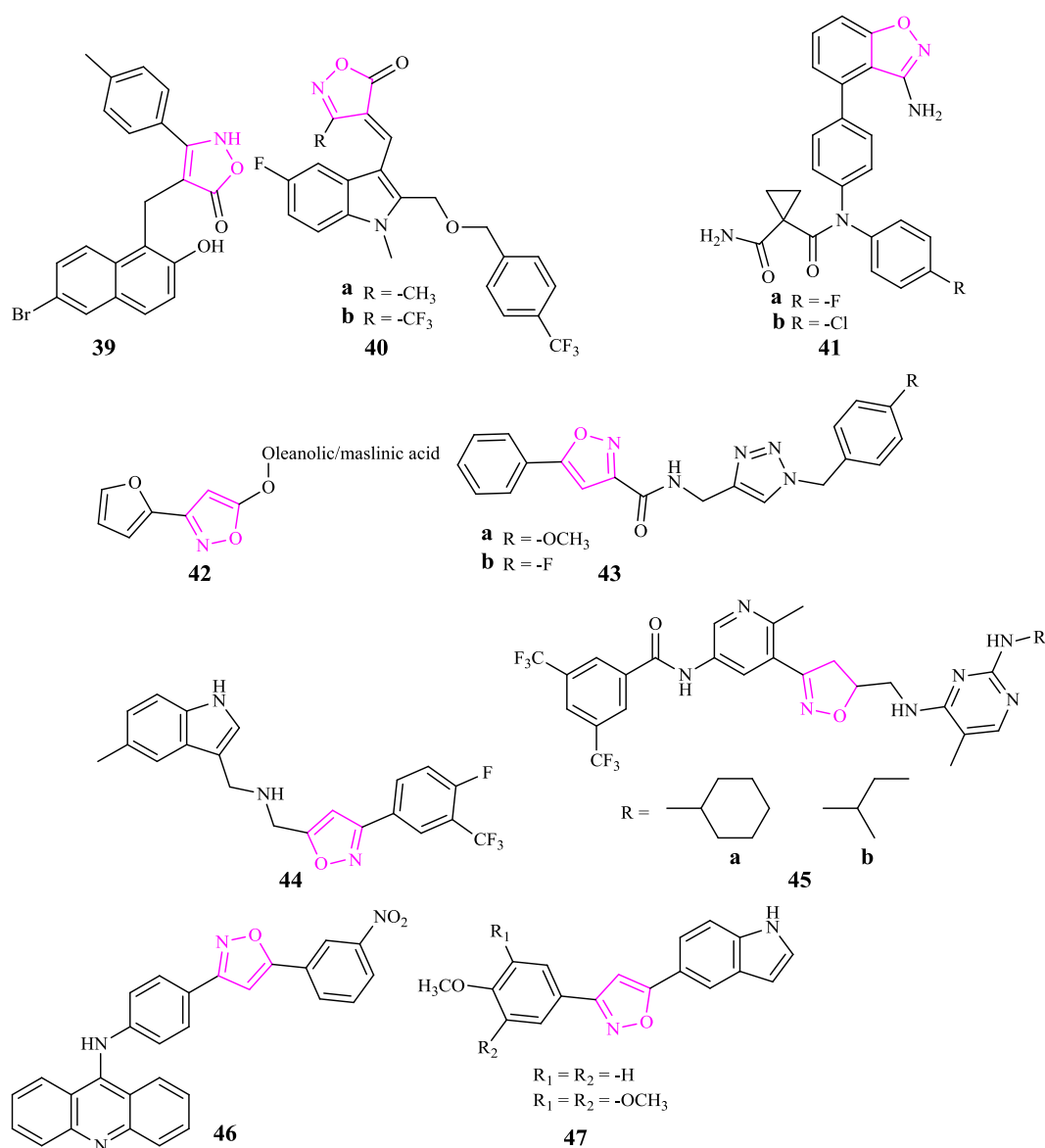
Fig. 10 Isoxazole derivatives showing anticancer activity (39–47)

Antimicrobial activity

RamaRao et al. (2011) synthesized 5-(heteroaryl)isoxazoles and evaluated for antibacterial activity against *E. coli*, *S. aureus* and *P. aeruginosa*. The isoxazoles substituted with 2-thienyl (48; Fig. 11) or 5-bromo-2-thienyl moieties (49; Fig. 11) in the 5-position displayed significant activity. Gautam and Singh (2013) synthesized a series of 4,5-dihydro-5-(substitutedphenyl)-3-(thiophene-2-yl)isoxazole and were tested in vitro for their antibacterial activity against *S. aureus*, *B. subtilis*, *E.coli* and *P. aeruginosa* and their antifungal activity against *A. niger* and *C. albicans* using disc diffusion method. The compound 50 (Fig. 11) was found to be highly active against *E.coli*, *P. aeruginosa* and *C. albicans* which may be attributed to its increased lipid solubility due to the presence of chloride on the aromatic ring. The rest of the compounds were found to be moderate to highly active. Basha et al. (2015) synthesized some thiazolyl isoxazoles and studied their antibacterial activity against *S. aureus*, *B. subtilis*, *K. pneumoniae* and *P. aeruginosa* and their antifungal activity against *A. niger* and *P. chrysogenum*. Thiazolyl iso-xazoles having phenyl ring (51; Fig. 11) substituted with chloro and nitro were found to be potential antibacterial agents against *S. aureus* and *A. niger*.

In (1,4-phenylene)bis(arylsulfonyl isoxazoles) series synthesized by Lavanya et al. (2014), the compound substituted with chloro on the aromatic ring (52; Fig. 11) exhibited excellent antibacterial activity (38 mm at 100 µg/mL) against *B. subtilis*, while rest of the compounds inhibited the spore germination against *P. chrysogenum* and
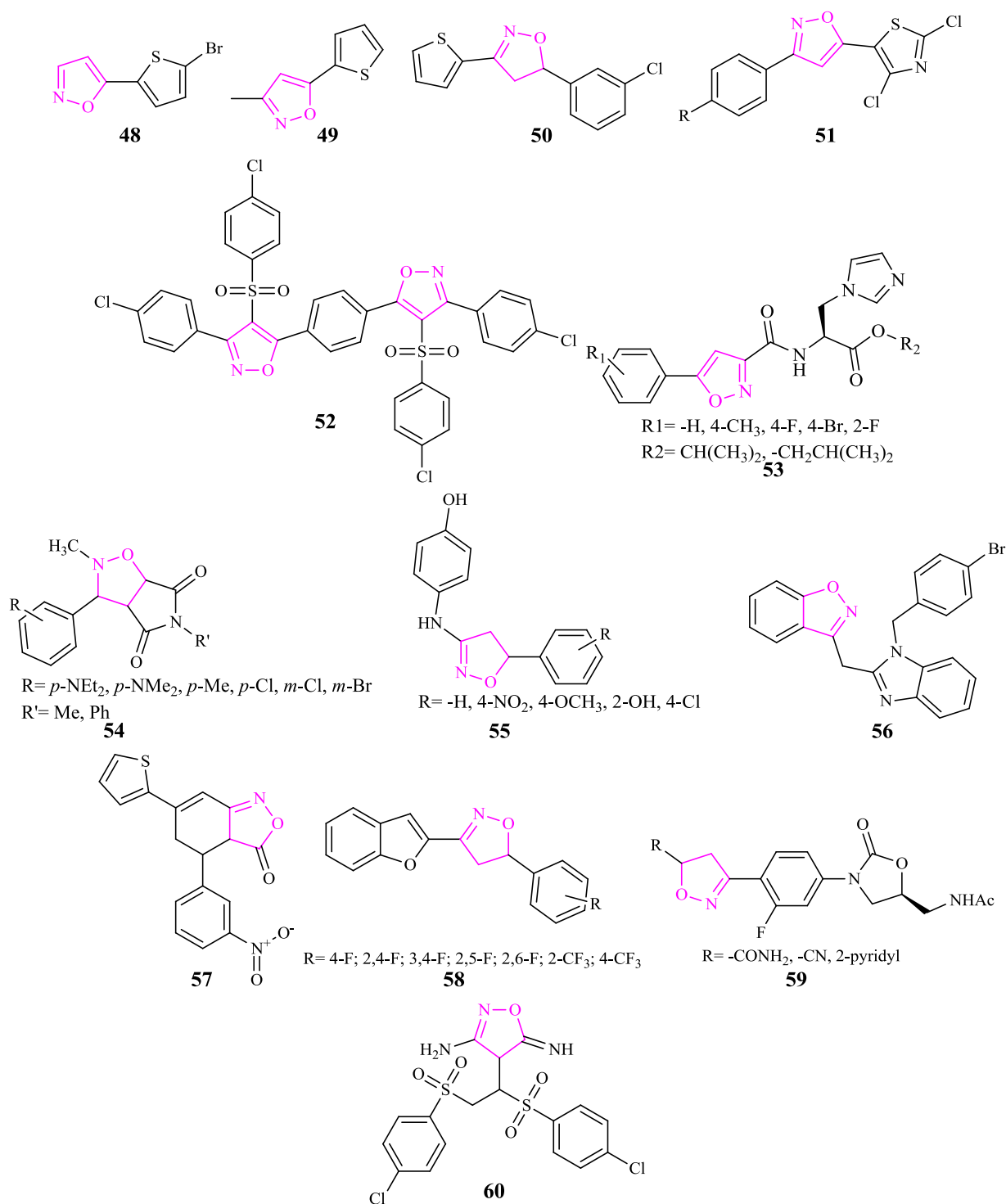
Fig. 11 Isoxazole derivatives showing antimicrobial activity (48–60)

A. niger. Zhao et al. (2017b) synthesized a series of aromatic heterocyclic derivatives and evaluated for in vitro antifungal activity. The compounds containing isoxazole nucleus (53; Fig. 11) improved the activity against *Aspergillus spp*., in particular. And the compounds having fluoro substituent at 2-position of aryl moiety displayed

remarkable activity against *Candida spp*., *C. neoformans*, *A. fumigatus* and fluconazole resistant *C. albicans* strain and exhibited weak inhibition profiles for various isoforms of human cytP450 and excellent blood plasma stability.

The 2,3,5-substituted perhydropyrrolo[3,4-*d*]isoxazole-4,6-diones (54; Fig. 11) have been synthesized by Agirbas

et al. (2007) by cycloaddition reaction of N-methyl-C-arylnitrones with N-substituted maleimides and screened for antibacterial activity. Most of them exhibited activity against *E. faecalis* and *S. aureus*. Sahu et al. (2009) synthesized a series of novel 4-(5′-substituted-aryl-4′,5′-dihydro-isoxazole-3′-yl-amino)phenols (**55**; Fig. 11) and screened for in vitro antibacterial activity against *S. aureus* and *S. typhi* and antifungal activity against *C. albicans* and *A. niger*. Compound bearing 4-Cl phenyl substitution at 5-position of isoxazole was found to be most potent antibacterial and antifungal agent of the series. Vaidya et al. (2007) synthesized a series of *N*-substituted-2-(benzo[*d*]isoxazol-3-ylmethyl)-1*H*-benzimidazoles and screened for antibacterial activity against *S. typhimurium* and *S. aureus*. Compounds exhibited good activity against *S. typhimurium* while poor activity against *S. aureus* except for compound **56** (Fig. 11) which was highly active even at 1 μg/mL. In another series, fused ring isoxazolinones displayed a wide range of antimicrobial activity. In particular, derivative **57** (Fig. 11) bearing thiophene ring was most potent against *B. subtilis* and *C. albicans* (Mazimba et al. 2014).

Chundawat et al. (2014) synthesized some fluorine-containing heterocycles incorporating benzofuran with dihydroisoxazoles (**58**; Fig. 11). The compounds were evaluated for their in vitro antibacterial activity against the Gram-positive bacteria *S. aureus*, *B. subtilis*, *S. pneumoniae*, *S. pyogenes*, the Gram-negative bacteria *E. coli*, *P. aeruginosa*, *S. typhi* and antifungal activity against the fungi *C. albicans*, *A. niger*, *A. clavatus*. All the compounds showed moderate to high activity against all tested bacterial strains and *C. albicans*. Weidner-Wells et al. (2004) synthesized a series of 5-substituted isoxazol-3-yl linked with oxazolidinone and screened for in vitro antimicrobial activity against susceptible and resistant Gram-positive organisms. Several analogs (**59**; Fig. 11) from this series were comparable to or more potent than linezolid in vitro and also exhibited in vivo activity in a lethal murine infection model but less than linezolid.

Padmaja et al. (2009) synthesized some aminoiminoisoxazole derivatives by Michael condensation of 2-(1′,2′-diaroylethyl)malononitrile and 2-(1,2-diarylsulfonylethyl)malononitrile with hydroxylamine hydrochloride. All the compounds possessed excellent antimicrobial activity against Gram-positive bacteria and good activity against Gram-negative bacteria with a maximum for the compound **60** (Fig. 11) having chloro substituent in the aryl moiety. These compounds also exhibited high antioxidant property in both nitric oxide and DPPH methods. Siddiqui et al. (2013) synthesized an isoxazole derivative **61** (Fig. 12) and evaluated for in vitro antibacterial and antifungal activity. It was found to be highly active against *P. aeruginosa* and *A. niger*, moderately active against *B. subtilis* and *E. coli* and poorly active against *S. aureus*. Srinivas et al. (2009)

synthesized a series of methylene-bis-4,6-diarylbenzo[*d*]isoxazoles and evaluated them against *C. albicans*, *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes*. Compounds **62, 63,** and **64** (Fig. 12) showed good activity against all the tested fungi that were almost equal to the standard Amphotericin B. The comparison of antifungal activity of dimeric compounds with monomeric compounds revealed that almost all the dimeric compounds showed enhanced activity than their monomeric analogs.

Srinivas et al. (2010) synthesized an another series of methylene-bis-tetrahydro[1,3]thiazolo[4,5-*c*]isoxazole and evaluated for their antifungal activity against *C. albicans*, *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* and further for nematicidal activity against *D. myceliophagus* and *C. elegans*. The compound **65** (Fig. 12) showed good activity against all the tested fungi, as well as significant nematicidal activity. Liu et al. (2014) synthesized a series of 2-(5-methyl-3-(4-chloro/trifluoromethylphenyl)isoxazol-4-yl)-5-arylamino-1,3,4-oxadiazoles and tested for in vitro antifungal activities against *B. cinerea* and *R. cerealis* by the mycelium growth rate method. All the compounds displayed moderate to high activities against *B. cinerea* whereas low activities against *R. cerealis*. Among them compounds **66a**, **66b**, and **66c** (Fig. 12) showed high activities against *B. cinerea* with the EC$_{50}$ value less than 20 μg/mL.

Brahmayya et al. (2013) synthesized some 5-aryl-4-methyl-3-yl-(imidazolidin-1-yl-methyl, 2-ylidene nitroimine) isoxazoles (**67**; Fig. 12) and tested them for fungicidal activity against *R. oryzae*, *C. tropicum* and *A. niger*. The compounds having halogen and methoxy groups emerged as good antifungals. Guo et al. (2015) synthesized 5-isoxazolyl substituted pyrimidine nucleosides and evaluated them for inhibitory activity on the growth of *L. donovani*. Aryl substituted isoxazole nucleosides (**68**; Fig. 12) showed stronger activity than alkyl substituted isoxazole nucleosides. And for aryl substituted isoxazole nucleosides, methyl and fluoro substituent at 4-position of the phenyl ring of the isoxazole moiety improved the antileishmanial activity. Mares et al. (2002) synthesized 3-methyl-5-aminoisoxazole-4-thiocyanate (**69**; Fig. 12) and studied on the dermatophyte *E. floccosum*. The compound **69** (Fig. 12) strongly inhibited the growth of the fungus in vitro and altered the ultrastructural morphology of the fungus.

Antitubercular activity

Kachhadia et al. (2004) prepared a series of 1-[*p*-(3′-chloro-2′-benzo(*b*)thiophenoylamino)-phenyl]-5-aryl-isoxazoles and screened for their antitubercular activity. Compounds **70a**, **70b**, and **70c** (Fig. 13) showed significant activity against MTB H$_{37}$Rv. Patel et al. (2014) synthesized coumarin-based isoxazoles and evaluated for their antimycobacterial activity against MTB H$_{37}$Rv using Lownstein-Jensen MIC method. Compound **71** (Fig. 13)
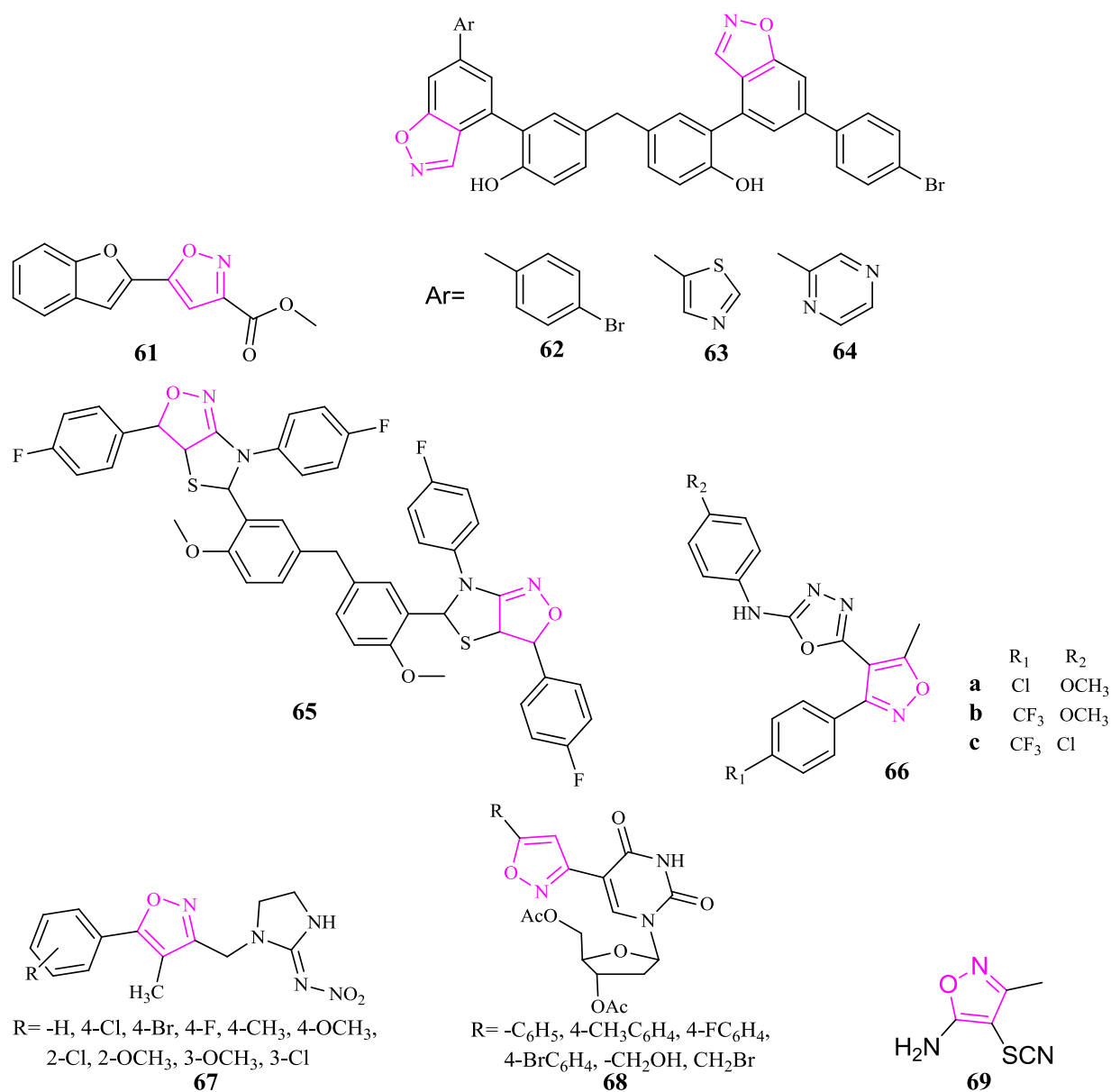
Fig. 12 Isoxazole derivatives showing antimicrobial activity (61–69)

bearing methoxy group exhibited good antimycobacterial activity with MIC of 62.5 μg/mL and 99% of inhibition while rest of the compounds showed MIC in the range of 100–1000 μg/mL. Changtam et al. (2010) synthesized iso-xazole analogs of curcumin and evaluated for anti-mycobacterial activity. The presence of *p*-methoxy and *p*-hydroxy groups on aromatic ring enhanced the activity. Compound **72** (Fig. 13) with mono-*O*-methyl curcumin isoxazole (MIC 0.09 μg/mL) was found to be 1131-fold more active than curcumin and approximately 18 and 2-fold more active than standard drugs kanamycin and isoniazid, respectively. Compound **72** (Fig. 13) also displayed high activity against multidrug-resistant MTB clinical isolates (MIC 0.195–3.125 μg/mL).

Joshi et al. (2016) synthesized pyrrolyl derivatives with isoxazole moiety and evaluated for activity against MTB. Compound **73** (Fig. 13) exhibited significant activity against H$_{37}$Rv strain and found to be non-toxic when tested for mammalian cell toxicity using A549 cancer cell line. Naidu et al. (2014) synthesized a series of 3-(4-(substituted sulfonyl)piperazin-1-yl)benzo[*d*]iso-xazole analogs and evaluated for their in vitro anti-tubercular activity against MTB H$_{37}$Rv strain. All the compounds exhibited MIC between 3.125 and 50 μg/mL. Compound **74** (Fig. 13) emerged as the most promising candidate for the series by inhibiting 99% growth of MTB H$_{37}$Rv strain at a concentration of 3.125 μg/mL and a selectivity of >130.
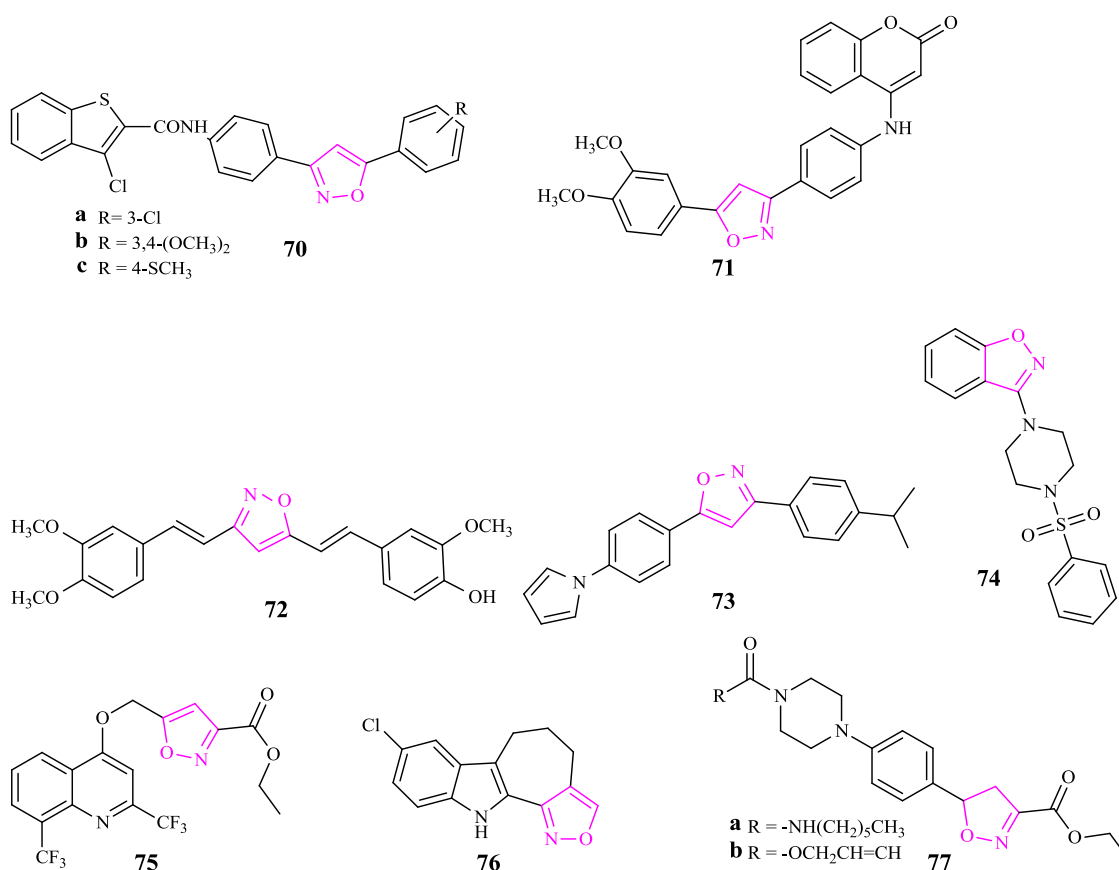
Fig. 13 Isoxazole derivatives showing antitubercular activity (70–77)

Mao et al. (2010) synthesized mefloquine-isoxazole carboxylic esters and evaluated for antitubercular activity. Compound **75** (Fig. 13) was found to possess excellent activity and specificity against MTB H$_{37}$Rv both intracellularly and extracellularly. The ester bio-isosteres of compound **75** were inactive as antitubercular agent suggesting that the ester may be acting as a prodrug. Yamuna et al. (2012) synthesized isoxazolo cyclohepta[*b*]indoles and screened for in vitro antimycobacterial against MTB H$_{37}$Rv. The maximum activity was found in compound **76** (Fig. 13) having a chloro substituent in the cyclohepta[*b*]indole moiety. This compound was found to be non-mutagenic and therefore biologically safe for intake. Rakesh et al. (2009) synthesized 3,5-disubstituted isoxazoline esters and evaluated them for anti-tuberculosis activity. Substitution of isoxazoline C-5 position with piperazyl-urea (**77a**; Fig. 13) and piperazyl-carbamate (**77b**; Fig. 13) improved anti-tubercular activity. However, replacement of ester group at C-3 position with bioisosteric groups led to complete loss of activity.

Antiviral activity

Due to the evolution of significant resistance toward antiviral drugs, the development of new drugs possessing potent antiviral activity is critical. Lee et al. (2009) synthesized some 5-isoxazol-5-yl-2′-deoxyuridines (**78**; Fig. 14) and evaluated their activity against 12 different viruses, namely HSV-1, HSV-2, HIV-1, HIV-2, Encephalomyocarditis virus, Coxsackie B3, vesicular stomatitis, three different influenza viruses (Taiwan, Seoul and Panama) and two corona viruses. All the compounds (**78**; Fig. 14) exhibited antiviral activities against all the tested virus except HIV, influenza and corona viruses. While some compounds were more active than the reference drugs but they were less selective. Deng et al. (2009) synthesized a series of alkenyldiarylmethanes with a benzo[*d*]isoxazole ring in place of metabolically unstable methyl ester moiety and screened for anti-HIV activity. All the compounds were found to inhibit HIV-1 Reverse Transcriptase but the compound **79** (Fig. 14) was most promising and a good alternative to hydrolytically unstable methyl esters.

Antidepressant activity

Patil and Bari (2013) synthesized isoxazolines incorporating indole and evaluated them for antidepressant activity by forced swim test in mice, and their locomotor activity was assessed using actophotometer. All the compounds showed

Fig. 14 Isoxazole derivatives
showing antiviral activity (**78**,
79)

R = H, Ac
R' = methyl, propyl
4-isopropylphenyl
4-tert-butylphenyl
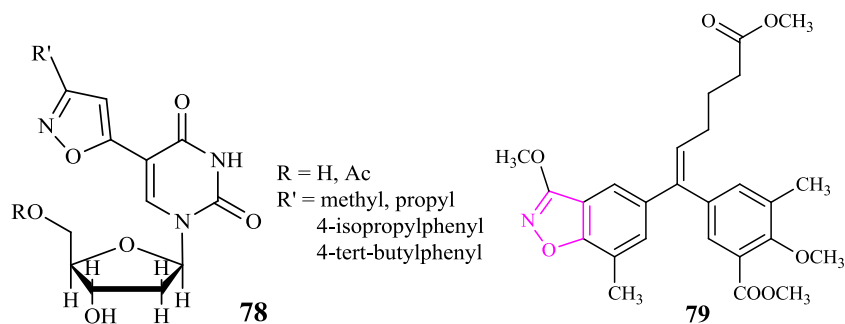
significant antidepressant activity with no significant change in locomotor activity. Compounds **80a** and **80b** (Fig. 15) emerged as potent antidepressants from this series when compared with reference drugs imipramine and fluoxetine indicating that introduction of an appropriate heterocyclic ring can lead to potent antidepressants. Andrés et al. (2003) reported the synthesis of enantiomeric pairs of 7-amino-3a,4-dihydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole derivatives. Compound **81** (Fig. 15) proved to be the most potent α$_2$-adrenoceptor blocker with potent serotonin (5-HT) reuptake inhibiting activity and thus acting as antidepressant agents. A further study (Andrés et al. 2007) showed that the compound **81** (Fig. 15) was more potent as 5-HT reuptake inhibitor than as α$_2$-adrenoceptor blocker both after subcutaneous and oral administration.

The α4β2 nicotinic acetylcholine receptors (nAChRs) are an attractive target for the development of novel antidepressants. Liu et al. (2011) synthesized several isoxazole analogs of Sazetidine-A (**82**; Fig. 15) by replacing the metabolically unstable acetylene of Sazetidine-A with metabolically stable isoxazole ring. Sazetidine-A interacts with α4β2-nAChRs as a partial agonist and possesses favorable antidepressant profiles. The compound **83** (Fig. 15) displayed selectivity, as well as excellent antidepressant behavioral activity measured by the mouse forced-swim test. Zhang et al. (2016) synthesized some hybrid compounds by combining substituted isoxazolyl side chains with N-pyridyldiamines as selective partial agonists for α4β2-nAChRs. Compound **84** (Fig. 15) displayed high binding selectivity towards α4β2 over α3β4-nAChRs and significant antidepressant activity in the forced swim test. Yu et al. (2012) synthesized a series of 5-alkoxy isoxazole as nAChRs ligands. Most of the compounds displayed selectivity for rat α4β2 over α3β4-nAChRs. Among them, compound **85** (Fig. 15) was highly selective and displayed potent antidepressant-like activity.

Olesen et al. (1998) synthesized a series of 3-((5-alkylamino-4-isoxazolyl)-1,2,5,6-tetrahydropyridine (**86**; Fig. 15) and evaluated for their affinity and selectivity for central nicotinic receptors. It was found that only the monoalkyl amino-substituted compounds had high affinity and selectivity for the central nicotinic receptors. The affinity

increased with increasing the alkyl side chain length up to propyl. Evaluation of these compounds in cell lines expressing nicotinic receptor subtypes showed that the compounds had up to 10-fold higher affinity for α4β2 receptor than α3β2 receptor subtype. Kumar et al. (2017) synthesized a series of 3,4,5-trisubstituted isoxazoles incorporating furan and piperazine moiety and evaluated for their antidepressant activity by Porsolt's forced swimming test on albino mice and antianxiety activity by plus maze method. Compounds **87a** and **87b** (Fig. 15) displayed significant antidepressant, as well as anti-anxiety activity. The molecular modeling studies showed good binding interactions of these compounds with the MAO-A (Fig. 16).

Anticonvulsant activity

Enhancement of GABA transmission by inhibiting GABA uptake has been proved to be an effective treatment for convulsions. Falch et al. (1999) synthesized some novel 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1,3-benzisoxazole derivatives and screened for GABA inhibitory and anticonvulsant activity. In the series of compounds, (*R*)-enantiomer of **88** (Fig. 17) in which primary amino group was converted to a secondary amino group, showed potent GABA inhibitory activity and was 12 times more potent as glial GABA uptake inhibitor than of neuronal GABA uptake. However, substitution of N-methyl group with N-ethyl group decreased the glial selectivity. Compound **88** potently protected Frings mice against audiogenic seizures when administered intracerebroventricularly. A series of *o*-substituted, *m*-substituted and *p*-substituted 4-phenyl-5-(4-piperidyl)-3-isoxazolols was synthesized by Frølund et al. (2007) and evaluated for antagonistic activity against GABA$_A$ receptor, a potential target for the treatment of epilepsy, anxiety and sleep disorders. The *m*-phenyl substituted compounds (**89a**, **89b**) and *p*-phenoxy (**89c**) substituted compounds (Fig. 17) displayed high affinity and antagonist potencies in the low nanomolecular range.

Clausen et al. (2005) synthesized a series of lipophilic diaromatic derivatives of (*R*)-4-amino-4,5,6,7-tetrahydrobenzo[*d*]isoxazol-3-ol and evaluated pharmacologically in vitro and in vivo for anticonvulsant activity.
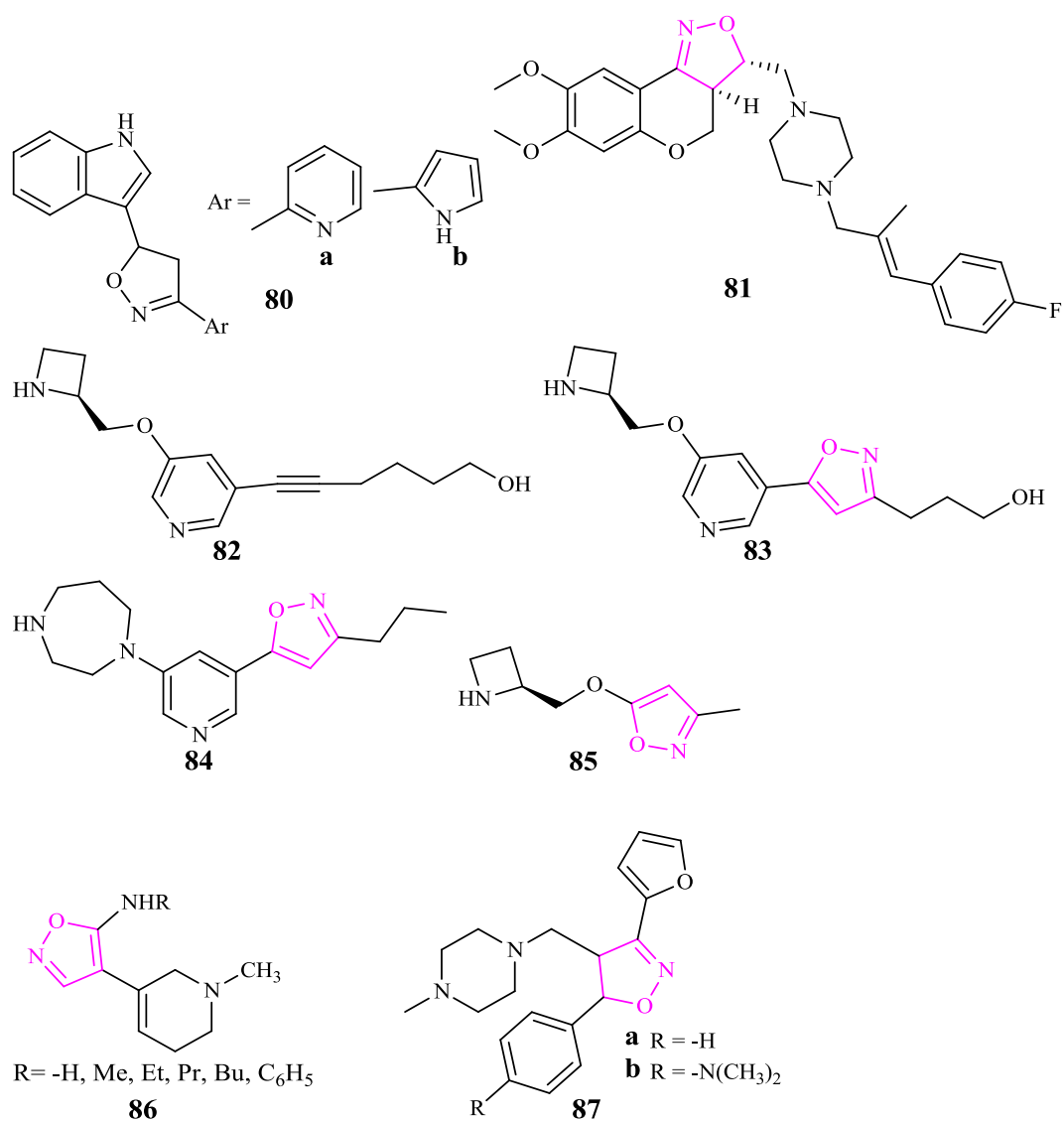
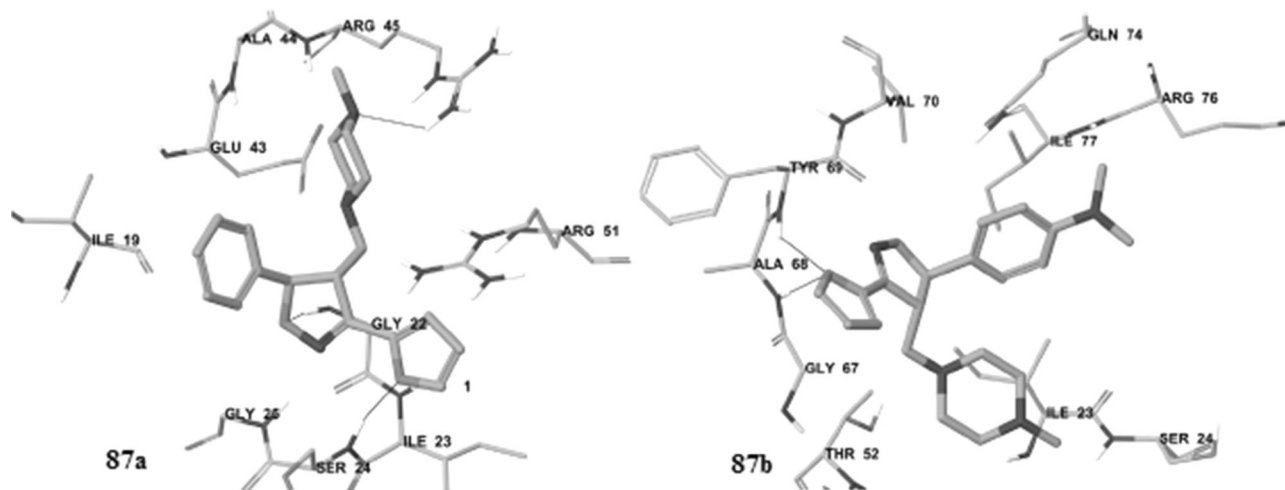**Fig. 15** Isoxazole derivatives showing antidepressant activity (**80–87**)

Fig. 16 Binding pattern and interaction of **87a** and **87b** at MAO-A (Kumar et al. 2017)
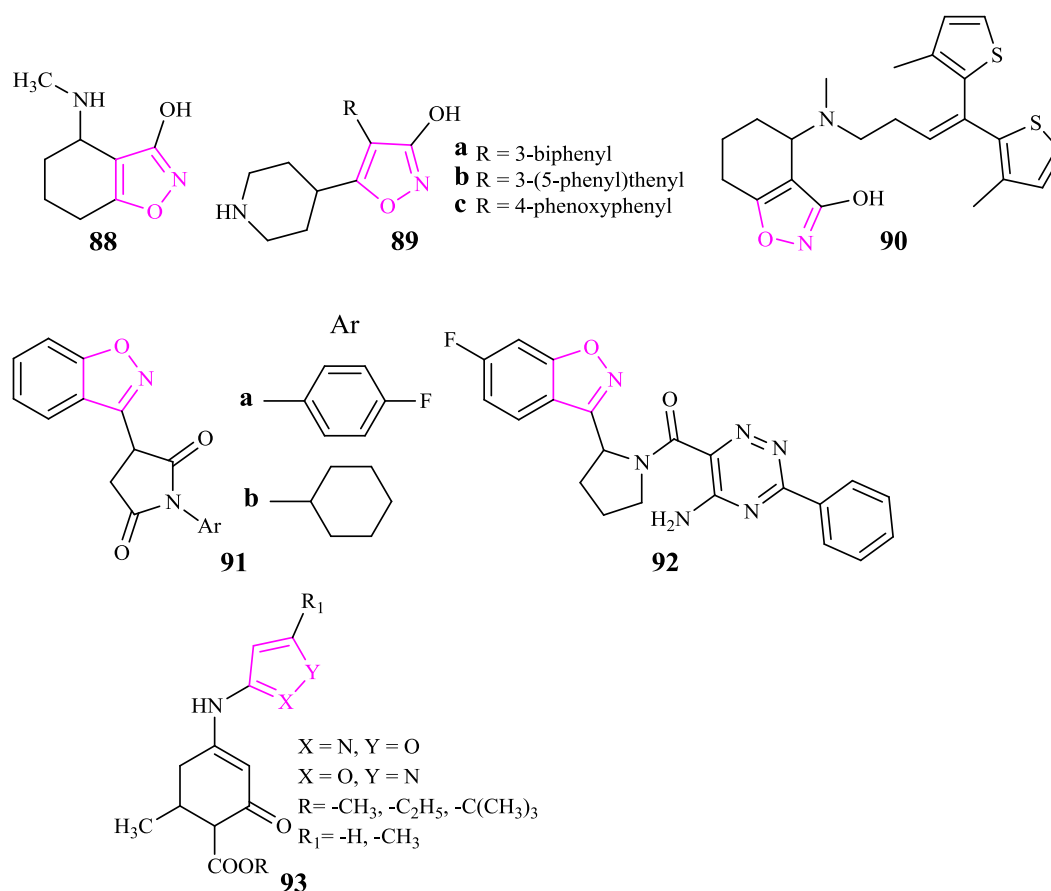
Fig. 17 Isoxazole derivatives showing anticonvulsant activity (**88–93**)

The compounds were effective as GABA uptake inhibitors and anticonvulsants showing that these compounds can cross BBB. The compound **90** (Fig. 17) appeared to be potent at GABA transporter 1 and 2. Malik et al. (2014) synthesized a series of 3-(benzo[*d*]isoxazol-3-yl)-*N*-substituted pyrrolidine-2,5-dione and screened through MES and scPTZ tests to find compounds affording protection against human generalized tonic-clonic seizures and generalized absence tonic-clonic seizures, respectively. Compound **91a** and **91b** (Fig. 17) were found to be most potent antiepileptogenic agents against MES and scPTZ tests, respectively.

Malik and Khan (2014) synthesized a series of (5-amino-3-substituted-1,2,4-triazin-6-yl) (2-(6-halo-substituted benzo[*d*]isoxazol-3-yl)pyrrolidin-1-yl)methanone derivatives and evaluated their anticonvulsant activities by the MES test. Compound **92** (Fig. 17) was found to be most potent and had the binding affinity with sodium channels in vitro. Eddington et al. (2002) synthesized a series of enaminones derived isoxazoles **93** (Fig. 17) by condensation of 1,3-diketo esters with 3- and 5-amino isoxazoles that led to a series of potent anti-maximal electroshock analogs.

Anti-Alzheimer activity

Huang et al. (2015) synthesized a series of azacyclic compounds with 5-substituted isoxazoline groups and evaluated their mAChR agonistic potential. A tetra-hydropyridine compound **94** (Fig. 18) substituted with 5-(2-pyrrolidin-1-yl)isoxazoline at 3-position exhibited potent and selective mAChR agonist activity. The compound **94** (Fig. 18) also possessed a disease-modifying role in Alzheimer's disease. Gutiérrez et al. (2013) synthesized some 3,5-disubstituted isoxazole derivatives, tested for their in vitro AChE inhibitory activity and performed their docking study. Compounds **95** and **96** (Fig. 18) emerged as potent AChE inhibitors. Anand and Singh (2012) synthesized pyrrolo-isoxazole benzoic acid derivatives as potential AChE for the management of Alzheimer's disease. All the derivatives displayed potent in vitro AChE inhibitory activity. Compound **97** (Fig. 18) was found to be most active which also ameliorated the scopolamine-induced amnesia in mice. JNK3 is exclusively found in the brain and play an important role in the brain to mediate neurodegeneration such as beta-amyloid
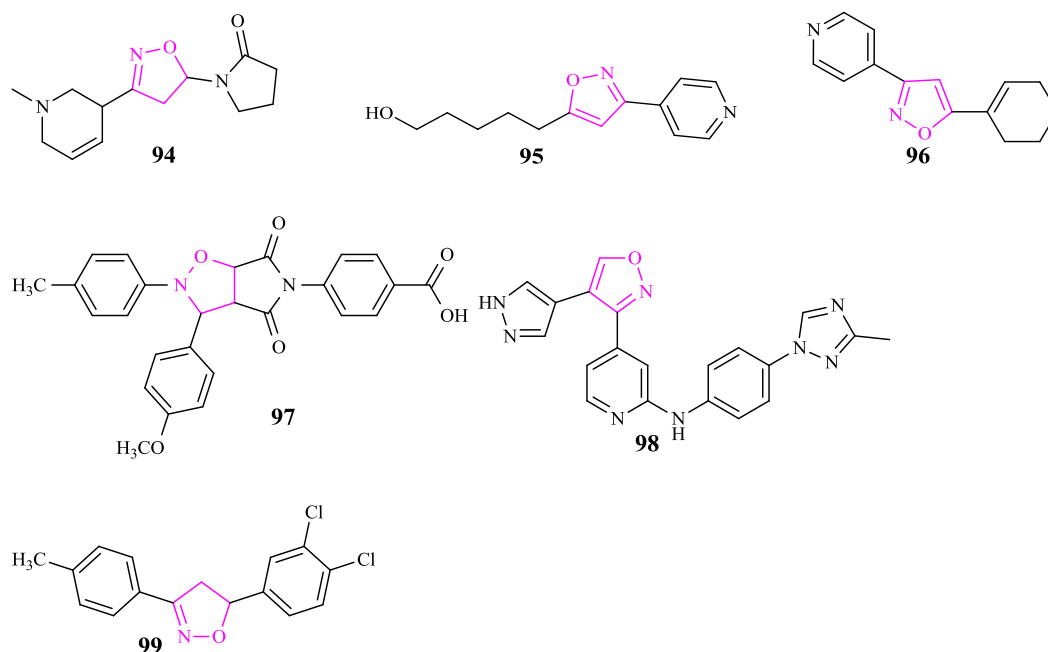
Fig. 18 Isoxazole derivatives showing antialzheimer's activity (94–99)
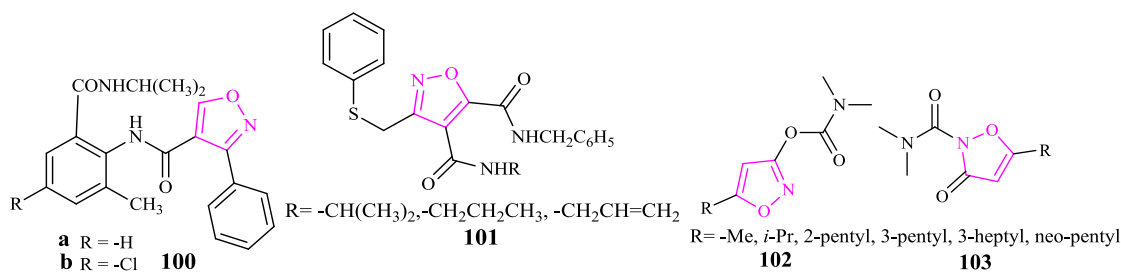
Fig. 19 Isoxazole derivatives showing insecticidal activity (100–103)

processing and neuronal apoptosis in Alzheimer's disease. Compounds with JNK3 inhibitory activity and selectivity over p38 can be potential therapeutics for neurodegeneration disorders as p38 inhibition leads to serious toxic effects. He et al. (2014) developed isoxazoles (98; Fig. 18) with improved JNK3 selectivity over p38 to treat neurodegenerative disorders. Meleddu et al. (2017) synthesized a series of 3,5-diaryl-4,5-dihydroisoxazoles to find MAO-B selective inhibitors to act as neuroprotective agents. None of the compounds inhibited MAO-A and compound 99 (Fig. 18) with a 3,4-dichlorophenyl moiety at position-5 of the dihydroisoxazole ring was the most active on MAO-B.

Insecticidal activity

Peng-fei et al. (2012) synthesized some novel phenyl substituted isoxazole carboxamides and evaluated for

insecticidal activities against *Mythimna separate* (oriental armyworm). All the compounds showed moderate insecticidal activity, out of which compounds 100a and 100b (Fig. 19) showed comparatively higher activities. SAR studies revealed that a combination of both aliphatic and aromatic amide moieties could improve the insecticidal activity. Yu et al. (2009) prepared a series of 3-(arylthio-methyl)isoxazole-4,5-carboxamides (101; Fig. 19) and evaluated for insecticidal activity using high-throughput screening (HTS) against *Spodoptera exigua* (beet armyworm) and *A. aegypti* (yellow fever mosquito). The results confirmed that 3,4,5-trisubstituted isoxazoles present a bioactive scaffold that can be utilized to design novel insecticides. To identify potential selective and resistance-breaking mosquitocides against the African malaria vector *Anopheles gambiae*, Verma et al. (2015) investigated the AChE inhibitory and mosquitocidal properties of isoxazol-3-yl dimethylcarbamates (102; Fig. 19), and the
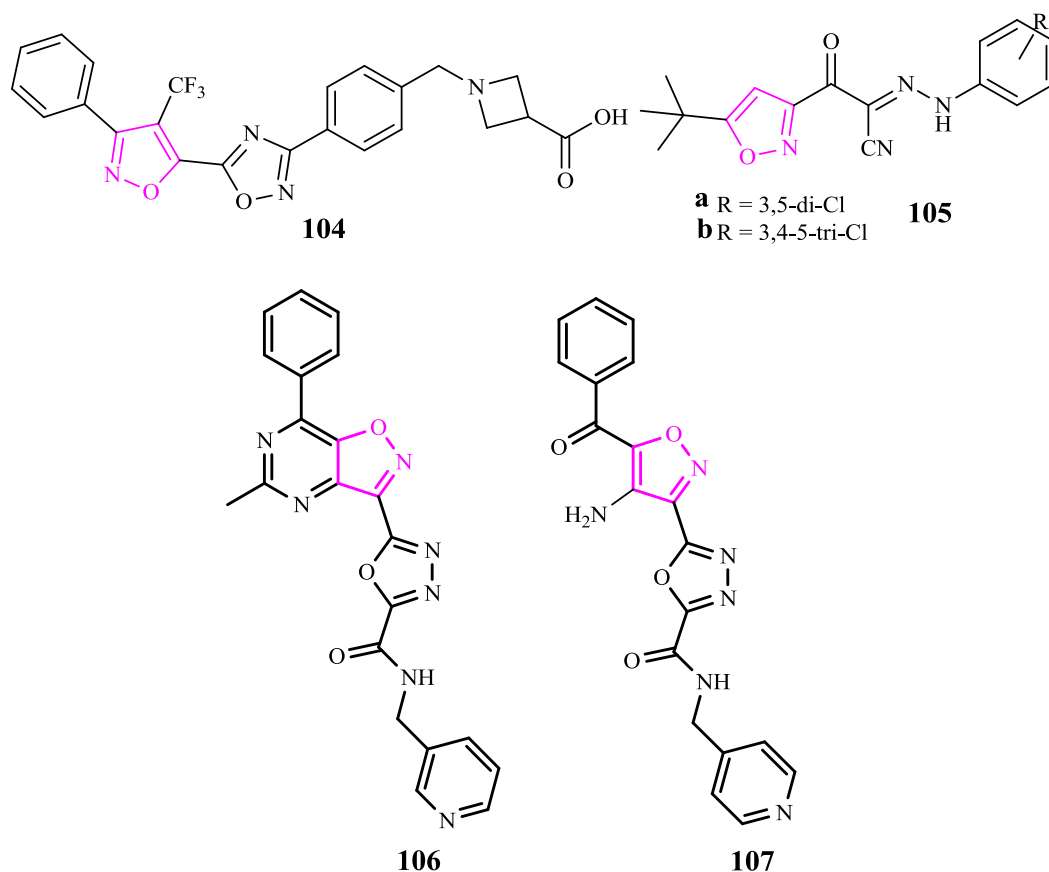
Fig. 20 Isoxazole derivatives showing immunosuppressant activity (**104–107**)

corresponding 3-oxoisoxazole-2(3*H*)-dimethylcarboxamide isomers (**103**; Fig. 19). In both series, compounds were found with excellent contact toxicity to wild-type susceptible (G3) strain and multiply resistant (Akron) strain mosquitoes that carry the G119S resistance mutation of AChE.

Immunosuppressant activity

Agonism of S1P$_1$, in particular, has been shown to play a significant role in lymphocyte trafficking from the thymus and secondary lymphoid organs, resulting in immunosuppression. Watterson et al. (2016) synthesized a series of isoxazoles derived from isoxazole-3-carboxylic acids and isoxazole-5-carboxylic acids to develop selective S1P$_1$ selective agonists. Compound **104** (Fig. 20) was emerged as a lead compound with good efficacy when administered orally in a rat model of arthritis (ED$_{50}$ 0.05 mg/Kg) and a mouse experimental autoimmune encephalomyelitis model of multiple sclerosis (ED$_{50}$ 0.05 mg/Kg). EPACs are involved in regulating a wide variety of intracellular physiological and pathophysiological processes like T-cell mediated immunosuppression (Almahariq et al. 2015).

Ye et al. (2015) synthesized a series of 2-(isoxazol-3-yl)-2-oxo-*N*'-phenyl-acetohydrazonoyl cyanide as EPAC antagonists. Compounds **105a** and **105b** (Fig. 20) have emerged as potential EPAC1 and EPAC2 inhibitors. The SAR studies revealed that further modifications at the 3-positions, 4-positions, 5-positions of the phenyl scaffold and the 5-position of the isoxazole moiety might give more potent EPAC antagonists. Wagner et al. (2008) synthesized isoxazolo[4,5-*d*]pyrimidine and tested for their effects on immune response in the mouse model. Compound **106** (Fig. 20) emerged as a universal inhibitor of immune response while compound **107** (Fig. 20) selectively suppressed the humoral immune response.

Antihyperglycemic, antiobesity, or hypolipidemic activity

Kafle and co-workers (Kafle et al. 2011; Kafle and Cho 2012) synthesized a series of isoxazolones to develop a potent inhibitor of PTP1B as an antiobesity and antihyperglycemic agent. PTP1B inhibition leads to prolongation of tyrosine phosphorylated stats of insulin and leptin receptors resulting in suppression of weight gain and
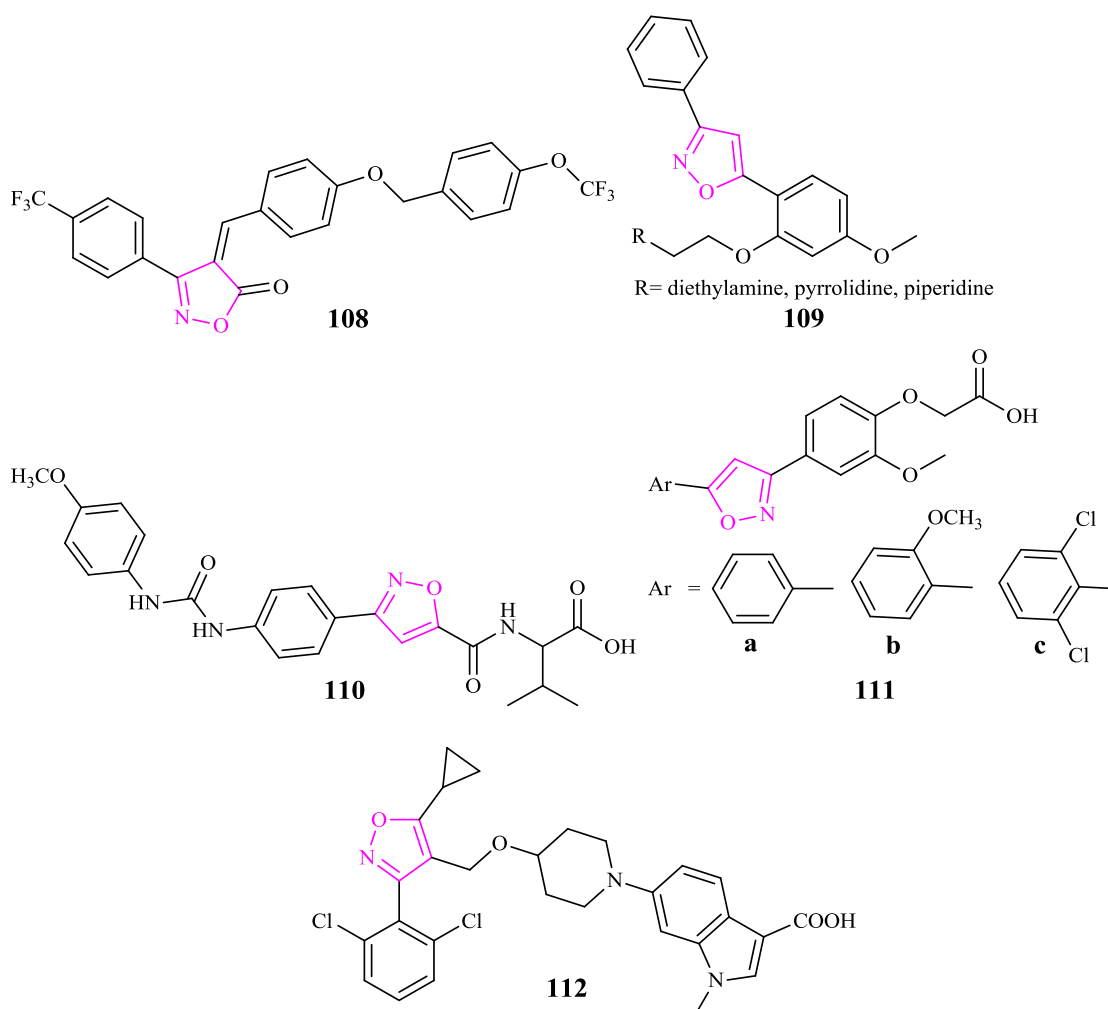
Fig. 21 Isoxazole derivatives showing antihyperglycemic, antiobesity or hypolipidemic activity (**108–112**)

augmentation of insulin sensitivity. Among them, compound **108** (Fig. 21) was the most potent and selective inhibitor of PTP1B with an IC$_{50}$ of 2.3 μM and can be considered as a promising lead compound for the control of obesity and hyperglycemia. Kumar et al. (2009) synthesized 3,5-diaryl isoxazole derivatives and screened them for in vivo anti-hyperglycemic and lipid-lowering activity. Some of the synthesized compounds **109** (Fig. 21) showed promising anti-hyperglycemic activity with moderate lipid-lowering activity. These compounds did not show any significant activity in PPAR and DPP-4 assay but exhibited the promising PTP1B inhibitory activity which revealed their mode of action. Jadhav et al. (2012) synthesized a series of compounds containing 3-phenyl isoxazoles and evaluated them for DGAT1 which is a promising target enzyme for obesity due to its involvement in the rate determining step of triglyceride biosynthesis. Compound **110** (Fig. 21) with an in vivo triglyceride reduction of 90% and IC$_{50}$ of 64 nM emerged as a promising anti-obesity agent.

Mokale et al. (2014) synthesized a series of 2-methyl-2-(substituted phenyl isoxazol)phenoxyacetic acid derivatives and evaluated them for in vivo hypolipidemic activity by triton induced hyperlipidemia in rats. Most of the compounds had the ability to lower the elevated lipid levels, amongst which **111a**; **111b**, and **111c** (Fig. 21) were found to be most active as compared to standard drug Fenofibrate. Further SAR studies revealed that isoxazole ring is important for hypolipidemic activity. FXR has been reported to have profound effects on plasma lipids in the animal model. Genin et al. (2015) discovered piperidinylisoxazole system as selective FXR agonist in vitro which showed robust lipid modulating properties lowering LDL and triglycerides while raising HDL in preclinical species and. The molecule LY2562175 (**112**; Fig. 21) is ultimately advanced to the clinical evaluation in humans due to its excellent lipid modulation profile in rodents, as well as acceptable pharmacokinetic properties.

Fig. 22 Isoxazole derivatives showing dopamine transporter inhibitor activity (**113**, **114**)
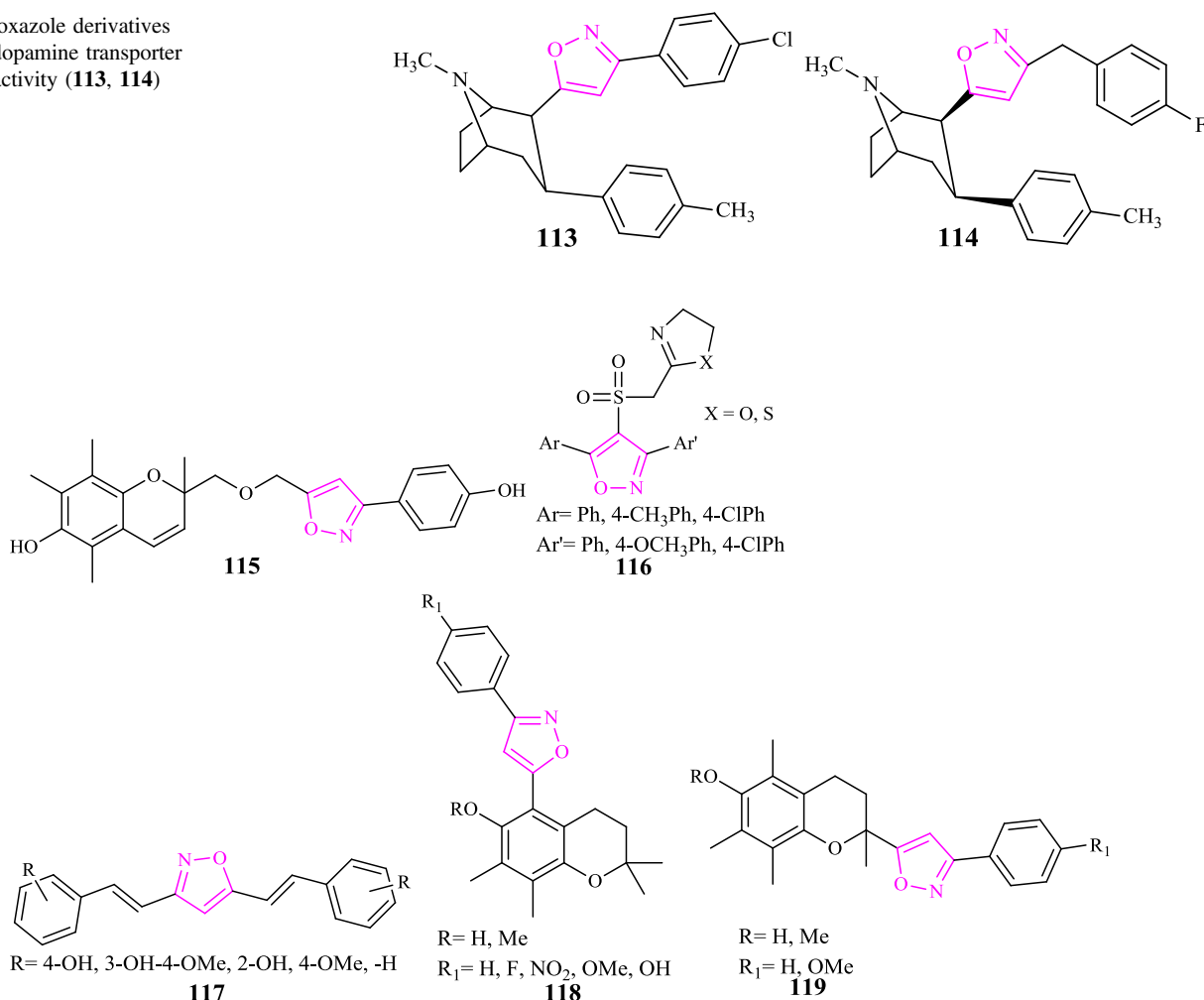
Fig. 23 Isoxazole derivatives showing antioxidant or antiageing activity (**115–119**)

Dopamine transporter inhibitory activity

Carroll et al. (2004) synthesized several 3β-(substituted phenyl)-2β-(3-substituted isoxazol-5-yl)tropanes and evaluated for their ability to inhibit radioligand binding at the monoamine (dopamine, serotonin and norepinephrine) transporters for the treatment of cocaine abuse. Most of the analogs were dopamine transporter selective, increase locomotor activity with slow onset and long duration of action. But the high dopamine transporter selective compound **113** (Fig. 22) surprisingly did not increase the locomotor activity that could be due to lack of brain penetration. Similarly, Jin et al. (2008) synthesized a series of 2β-[3′-(substituted benzyl)isoxazol-5-yl]- and 2β-[3′-methyl-4′-(substituted phenyl) isoxazol-5-yl]-3β-(substituted phenyl)tropanes. These compounds were evaluated for affinities at monoamine (dopamine, serotonin and norepinephrine) transporters

for the treatment of cocaine abuse. All the tested compounds were found to be relatively selective for dopamine transporter. The compounds of former series exhibited 3-fold to 25-fold higher affinities at dopamine transporter. Among them, compound **114** (Fig. 22) was most potent and dopamine transporter selective analog.

Antioxidant/antiageing activity

Koufaki et al. (2014) synthesized a series of 3,5-disubstituted isoxazoles and evaluated their cytoprotective and antiageing properties in terms of stress resistance in human primary fibroblasts (in vitro model) and with the extended longevity of the nematode *C. elegans* (in vivo model). Compound **115** (Fig. 23) bearing a phenolic group and a 6-OH chroman group was revealed to be a potent antioxidant and anti-ageing agent. Padmaja et al. (2011) prepared bis

Fig. 24 Isoxazole derivatives showing antistress activity (**120**–**122**)
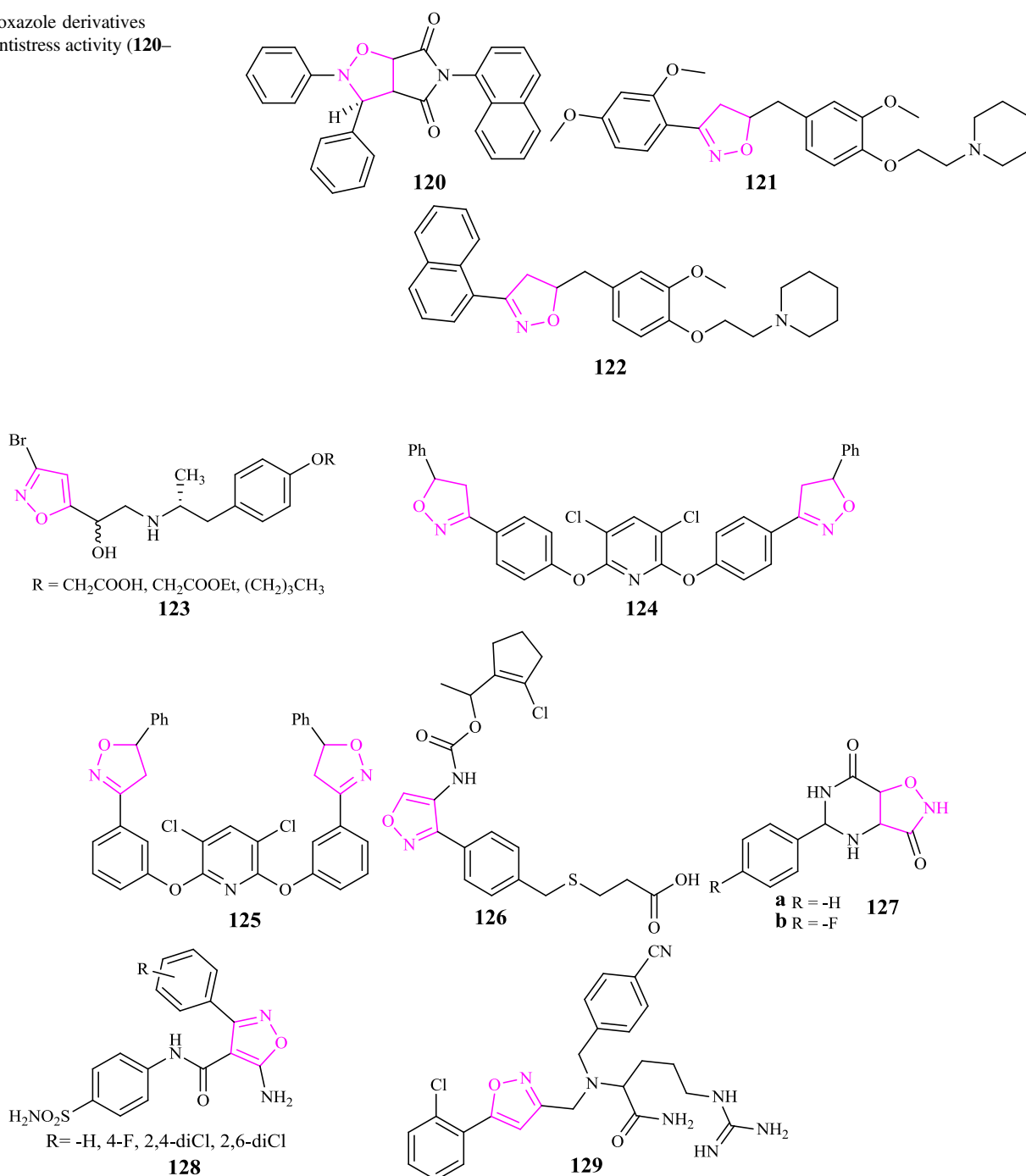
Fig. 25 Isoxazole derivatives showing miscellaneous activity (**123**–**129**)

heterocycles-oxazolyl/thiazolylsulfonylmethyl isoxazoles (**116**; Fig. 23) and evaluated for antioxidant activity. It was observed that the compounds having isoxazole in combination with oxazoline exhibited high antioxidant activity. The presence of electron donating substituent on the aromatic ring enhanced the activity.

Sherin and Rajashekharan (2016) synthesized 3,5-bis (styryl)isoxazoles (**117**; Fig. 23) derived from curcuminoids

by mechanochemical grinding of the curcuminoids with hydroxylamine hydrochloride catalyzed by glacial acetic acid and evaluated for antioxidant activity by DPPH, FRAP and β-carotene assays. The presence of hydroxyl and methoxy groups on the terminal aryl moieties of 3,5-bis (styryl)isoxazoles improved the antioxidant activity. Koufaki et al. (2011) synthesized a series of 2-isoxazolyl or 5-isoxazolyl chromans (**118**, **119**; Fig. 23) with the aim to

Table 2 SAR displaying different substituents at 3, 4, and 5-positions of isoxazole moiety for various biological activities

Activity	Groups at 3-position	Groups at 4-position	Groups at 5-position
Analgesic	Methyl, carboxy	Unsubstituted	Substituted phenyl
Anti-inflammatory	Substituted phenyl	Substituted phenyl, pyridine	Indole, isopropyl
Anticancer	Substituted phenyl, furan, indole	Unsubstituted, arylsulfonyl, arylamido	Amino, arylamido, substituted phenyl, indole, thiazole, quinoline
Antimicrobial	Substituted phenyl, thiophene, benzofuran, amino	Arylsulfonyl, thiocyanate, 2-amino oxadiazole	Amino, halogen substituted phenyl, thienyl, thiazole
Antidepressant	Pyridine, pyrrole	Unsubstituted, piperazine	Indole, pyridine, substituted amine
Anticonvulsant	Hydroxyl, pyrrolidine	Substituted phenyl	piperidyl
Anti-Alzheimer	Substituted phenyl, pyridine	Unsubstituted, pyrazole	Substituted phenyl, Long chain alkyl, cyclohexene, pyrrolidine
Immunosuppressant	Substituted aryl	Unsubstituted, trifluoromethyl, amino	*tert*-butyl, oxadiazole

discover neuroprotective agents with much lower cytotoxicity. The neuroprotective activity was evaluated against oxidative stress-induced death of neuronal H22 cells (mouse hippocampal cell line). The majority of them displayed high in vitro neuroprotective activity with EC_{50} below 1 μM and lacked cytotoxicity.

Antistress activity

Badru et al. (2012) synthesized a series of pyrrolo-isoxazole derivatives via 1,3-dipolar cycloaddition of azomethine N-oxides with N-(α-naphthyl)maleimide. Compound **120** (Fig. 24) exhibited significant anti-stress activity in immobilization stress-induced increase in non-social behavior. Maurya et al. (2011) synthesized 3,5-disubstituted isoxazolines and evaluated their anti-stress potential under acute stress condition in relation to peripheral and biochemical changes. Some compounds **121** and **122** (Fig. 24) displayed protective effects against acute stress-induced elevation in gastric ulceration, adrenal hypertrophy, hyperglycemia, plasma creatine kinase activity, and corticosterone levels.

Miscellaeneous activities

Dallanoce et al. (2007) synthesized three pairs of stereo-isomeric 3-bromo-isoxazolyl amino alcohol derivatives **123** (Fig. 25) and evaluated for their binding affinity at human β1-ARs, β2-ARs, and β3-ARs in membranes from Chinese hamster ovary cells stably transfected with the respective receptor subtype. The highest efficacy (70–90%) was observed at β2-ARs whereas all compounds behaved as

partial agonists (30–60%) at the β3-subtype and the lowest (15–35%) was found at β1subtype. Shailaja et al. (2011) synthesized a series of 3,5-disubstituted-4,5-dihydroisoxazoles and 3,4,5-trisubstituted isoxazoles and evaluated for their action on isolated frog heart. All the test compounds moderately reduced the heart rate, cardiac output, and force of contraction and compounds **124** and **125** (Fig. 25) showed better inhibition of sodium exchange ion on isolated frog heart studies.

Yamamoto et al. (2007) synthesized isoxazole derivatives and evaluated for LPA antagonistic activity to find potent drugs to treat liver fibrosis. Compound **126** (Fig. 25) exhibited high inhibitory activity at LPA receptor and was expected to be a potent drug candidate for the treatment of liver fibrosis. Wagner et al. (2004) synthesized 5-alkyl and 5-arylisoxazolo[4,5-*d*]pyrimidinones structurally similar to hypoxanthine and evaluated for anxiolytic activity. Compounds **127a** and **127b** (Fig. 25) displayed the approximately same anxiolytic activity as that of diazepam at the non-sedative dose.

Altug et al. (2017) synthesized a series of sulfonamide based 5-amino isoxazole derivatives (**128**; Fig. 25) and screened for their CA inhibitory properties against four human isoforms: hCA I, hCA II, hCA IV, and hCA VII. All the compounds exhibited excellent inhibitory activity against the cytosolic isoform hCA II, an antiglaucoma drug target. Batra et al. (2002) utilized 3-substituted-phenyl-5-isoxazole carboxaldehydes to generate isoxazole-based combinatorial libraries on solid phase through automation. All the compounds were evaluated for their antithrombotic activity in vivo. Compound **129** (Fig. 25) was found to be most potent with 90% protection against bleeding time.

Conclusion

The present review demonstrates the synthesis and structural modifications of isoxazoles. Isoxazole is a versatile building block in many biologically active compounds, and its easy synthesis offers the structure activity studies of various substitutions on this pharmacophore as illustrated in Table 2. This review is endeavoring to find potential future directions in the development of more potent and specific analogs of isoxazole-based compounds for the biological target. The information of the isoxazole based heterocycles illustrated in this review will not only update medicinal chemists with recent findings of biological activities of isoxazoles but also encourage them to use this promising scaffold for the design of novel molecules to identify many more biologically active isoxazoles for the benefit of humanity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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