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Synthesis of hybrid molecules of isoxazole derivatives in search of new anticancer drugs – A review

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ABSTRACT

Nowadays, the term 'hybrid drugs' come to have recognition in the pharmaceutical field as they can potentially overcome most of the pharmacokinetic drawbacks and used in the treatment of many diseases. Discovery of hybrid anticancer drugs with high therapeutic activity leads to trigger two or more cytocidal pharmacological mechanisms of action acting in synergy to inhibit tumor growth. The review showcases the research that is at the prime edge of hybrid anticancer drug discovery. Isoxazole and its derivatives are an important class of heterocyclic compounds show a broad spectrum of biological activities which have made them significant structures. A modification in their structures by incorporating heterocyclic ring to the isoxazole moiety has offered a high degree of diversity that has manifest beneficial for the discovery of hybrid molecules of isoxazole derivatives with potent activity. Thus this review explains the various synthesis of different isoxazole hybrid molecules and their evaluation of the anticancer activity.

Keywords— *Hybrid molecules, Isoxazole derivatives, Synthesis, Anticancer activity*

1. INTRODUCTION

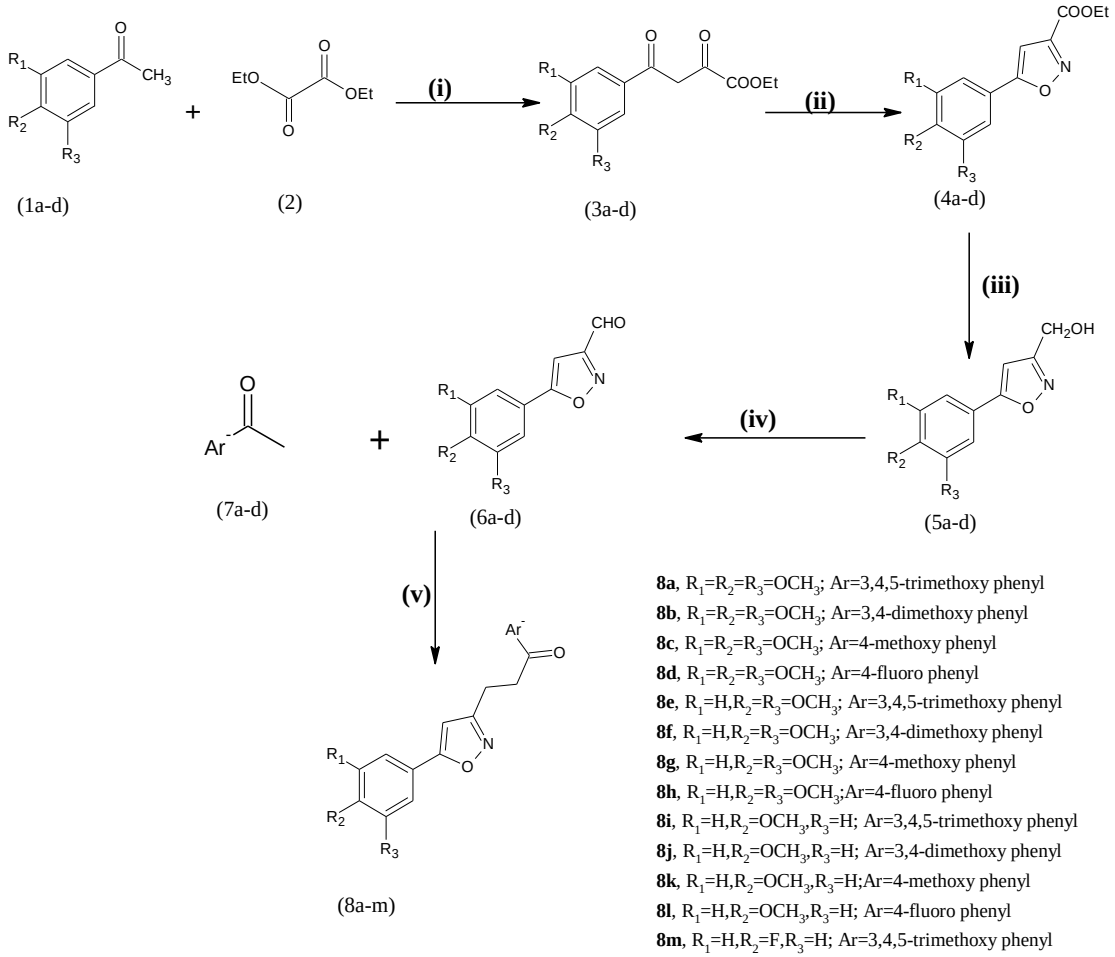
A new series of hybrid molecules are developed by chemical hybridisation in which two drug pharmacophores are clubbed in to a single molecule with multifunctional or conjugated action.Hybrid molecules may also present synergestic effect compared to the discrete pharmacophores. Derivatives of isoxazoles containing fused heterocycles played an important role in the heterocyclic chemistry and offered a high degree of diversity that has manifest useful for the progress of new therapeutic agents having significant potency and lesser toxicity. Heterocycle linked isoxazole derivatives rising prevalence importance in medicinal chemistry so a remarkable amount of research effort has been fascinated on this nuclei.A new series of diverse isoxazole linked heterocycle hybrids are clinically preferred to traditional cytotoxic treatment.They also possess various range of biological activities such as anticonvulsant, anti-tubercular, anthelmintics,antioxidant ,anti-inflammatory,antimicrobial and so on. Modification in their structure has emerged as powerful technique for bring on new molecules useful for drug discovery.

The main objective of this review article is to collect all possible methods that are used to synthesize isoxazole derivatives contain heterocycle by conventional method and to evaluate anticancer activity of selected compounds that exhibit a spectacular activity against the different cancer cell lines.

2. SYNTHESIS

Thiriveedhi et al., synthesized thirteen novel hybrid molecules of isoxazole derivatives **(8a-m)** by the Claisen-Schmidt condensation of suitable substituted acetophenones **(1a-d)** with isoxazole aldehydes. The key intermediates 5-substituted phenyl-isoxazole-3-carbaldehydes **(6a-d)** were prepared in four sequential steps.The obtained carbaldehydes were condensed with 1-(substituted phenyl) ethanone **(7a-d)** in the presence of 10% aqueous sodium hydroxide solution to form isoxazole chalcone compounds as shown in figure 1.

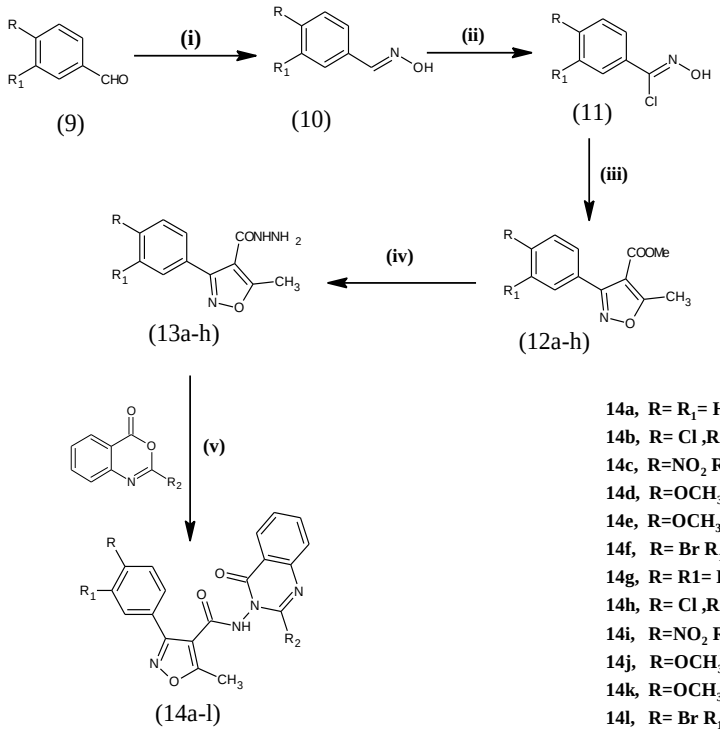
Twelve novel isoxazole synchronized quinazolinone derivatives **(14a-l)** were designed and synthesized by Radhika tumma et al., condensation of different 3-aryl-5-methyl isoxazole-4-carbohydrazides **(13a-h)** with 2-phenyl/2-methyl-(4H) 3, 1-benzoxazine-4-ones to give the target compounds. The synthesis was accomplished as shown in figure 2.



8a, $R_1=R_2=R_3=OCH_3$; Ar=3,4,5-trimethoxy phenyl
8b, $R_1=R_2=R_3=OCH_3$; Ar=3,4-dimethoxy phenyl
8c, $R_1=R_2=R_3=OCH_3$; Ar=4-methoxy phenyl
8d, $R_1=R_2=R_3=OCH_3$; Ar=4-fluoro phenyl
8e, $R_1=H,R_2=R_3=OCH_3$; Ar=3,4,5-trimethoxy phenyl
8f, $R_1=H,R_2=R_3=OCH_3$; Ar=3,4-dimethoxy phenyl
8g, $R_1=H,R_2=R_3=OCH_3$; Ar=4-methoxy phenyl
8h, $R_1=H,R_2=R_3=OCH_3$;Ar=4-fluoro phenyl
8i, $R_1=H,R_2=OCH_3,R_3=H$; Ar=3,4,5-trimethoxy phenyl
8j, $R_1=H,R_2=OCH_3,R_3=H$; Ar=3,4-dimethoxy phenyl
8k, $R_1=H,R_2=OCH_3,R_3=H$;Ar=4-methoxy phenyl
8l, $R_1=H,R_2=OCH_3,R_3=H$; Ar=4-fluoro phenyl
8m, $R_1=H,R_2=F,R_3=H$; Ar=3,4,5-trimethoxy phenyl

(i) Na metal,EtOH,rt;4-5h (ii) $NH_2OH.HCl$,EtOH,reflux,2-3h (iii)LAH,THF,rt,2-3h (iv)IBX,DMSO,0^0C,2-3h (v)10% aq.NaOH,1-2h,rt

Fig. 1: Synthesis of novel hybrid isoxazole derivates

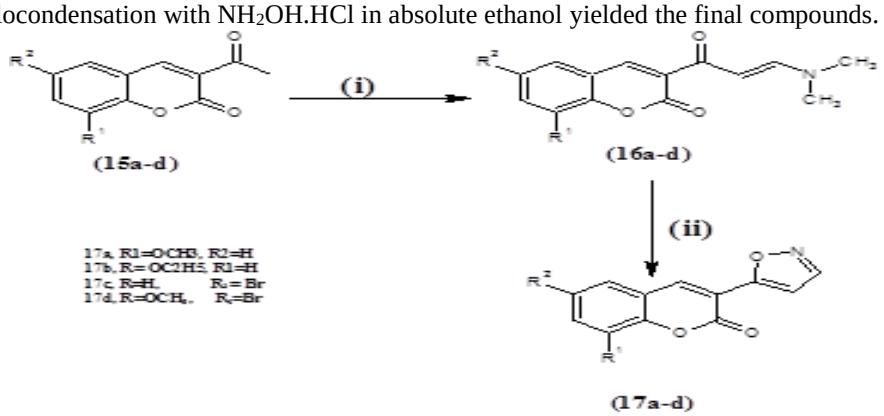


14a, R= R_1= H R_2 = 2-phenyl(4H)3,1-benzoxazine 4-one
14b, R= Cl ,R_1=H ,R_2 = 2-phenyl(4H)3,1-benzoxazine 4-one
14c, R=NO_2 R_1= H ,R_2 = 2-phenyl(4H)3,1-benzoxazine 4-one
14d, R=OCH_3 , R_1=H ,R_2 = 2-phenyl(4H)3,1-benzoxazine 4-one
14e, R=OCH_3 , R_1= OCH_3 ,R_2 = 2-phenyl(4H)3,1-benzoxazine 4-one
14f, R= Br R_1=H ,R_2 = 2-phenyl(4H)3,1-benzoxazine 4-one
14g, R= R1= H ,R_2 = 2-methyl(4H)3,1-benzoxazine 4-one
14h, R= Cl ,R_1=H ,R_2 = 2-methyl(4H)3,1-benzoxazine 4-one
14i, R=NO_2 R_1= H ,R_2 = 2-methyl(4H)3,1-benzoxazine 4-one
14j, R=OCH_3 , R_1=H ,R_2 = 2-methyl(4H)3,1-benzoxazine 4-one
14k, R=OCH_3 , R_1= OCH_3 ,R_2 = 2-methyl(4H)3,1-benzoxazine 4-one
14l, R= Br R_1=H ,R_2 = 2-methyl(4H)3,1-benzoxazine 4-one

(i)$NH_2OH.HCl$,NaOH/CH_3COONa,CH_3OH,Reflux 4-5hr
(ii) N-Chloro succinamide,DMF,Stirring 12hrs
(iii)Ethylacetoacetate,MeOH,NaOH,Stirring
(iv)$NH_2NH_2.H_2O$,reflux 12hrs
(v)2-phenyl/2-methyl(4H)3,1-benzoxazine4-one,pyridine,reflux 48hrs

Fig. 2: Synthesis of novel isoxazole synchronized quinazlinone derivates

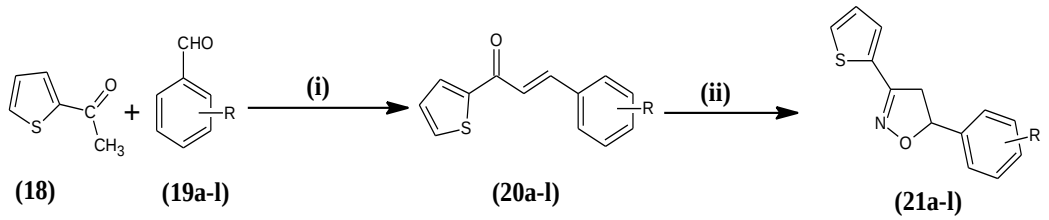
Khaled et al., synthesized four new derivatives of isoxazole containing coumarin moiety **(17a-d)** by the treatment of 3-acetyl coumarin derivatives **(15a-d)** with Dimethyl Formamide Dimethyl Acetal (DMFDMA) in toluene afforded enamine derivatives **(16a-d)** which on cyclocondensation with $NH_2OH.HCl$ in absolute ethanol yielded the final compounds.



(i)Dimethylformamide dimethyl acetal(DMFDMA),toluene
(ii) $NH_2OH.HCl$,Absolute ethanol

Fig. 3: Synthesis of isoxazole containing coumarin derivatives

Jagdish et al., framed an idea of incorporating thiophene moiety in to isoxazole derivative inorder to generate compounds with better pharmacological activity. It started with the condensation of 2-acetyl thiophene **(18)** with the various aromatic aldehydes **(19a-l)** in the presence of base to furnish the respective chalcones .Reaction between **(20a-l)** and hydroxylamine HCl in the presence of dry pyridine offered respective thiophene incorporated isoxazole derivatives **(21a-l)**.

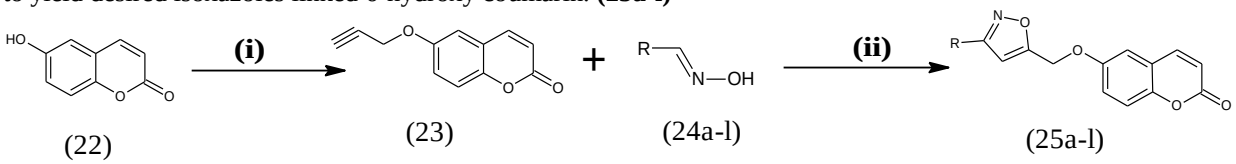


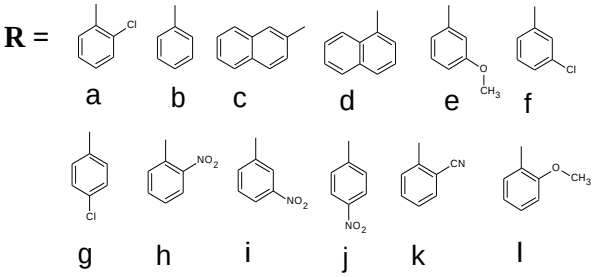
21a =4-H **21g= 4-OH**
21b= 2-Cl **21h= 4-CH_3**
21c= 3-Cl **21i= 4-OCH_3**
21d= 4-Cl **21j= 4-NH_2**
21e= 4-Br **21k= 4-$N(CH_3)_2$**
21f= 4-f **21l= 3,4-$(OCH_3)_2$**

(i) KOH,Ethanol
(ii)$NH_2OH.HCl$,Pyridine

Fig. 4: Synthesis of isoxazole contacting thiophene derivates

A new series of diverse isoxazoles linked 6-hydroxy coumarin were synthesized by Shakeel et al., using click chemistry approach.The precursor **(22)** was subjected to alkylation at the hydroxyl position using propargyl bromide in the presence of a base to furnish 6-(prop-2-ynyl-oxy)-2H-chromen-2-one.It was eventually subjected to 3+2 cycloaddition with various organic oximes **(24a-l**) to yield desired isoxazoles linked 6-hydroxy coumarin. **(25a-l)**





(i)Propargyl bromide,K_2CO_3,Acetone,rt,1 hr
(ii)K_2CO_3,N-chlorosuccinimide,THF,rt,1-2hr

Fig. 5: Synthesis of isoxazole linked 6-hydroxy coumarin derivates

Reddy et al., was carried out the synthesis of isoxazole tagged 2H –chromene derivatives from salicyaldehyde and ethyl-4,4,4-trifluoromethyl)-2H-chromene-3-carboxylate.(**28**) was then treated with propagyl bromide in acetone using K_2CO_3 as a base and yield o-propargylated chromene derivatives which was again reacted with different aryl aldoximes to give isoxazole functionalized 2H-chromene intermediate (**31a-g**)

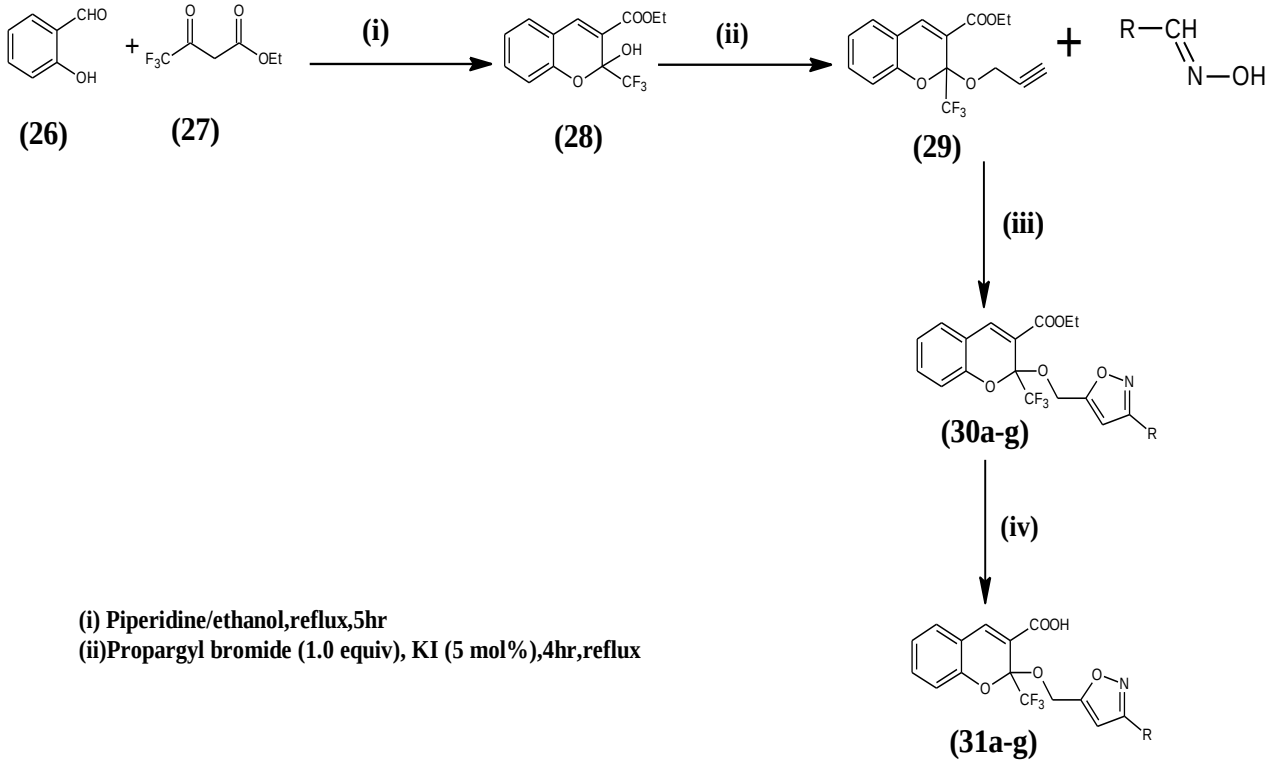
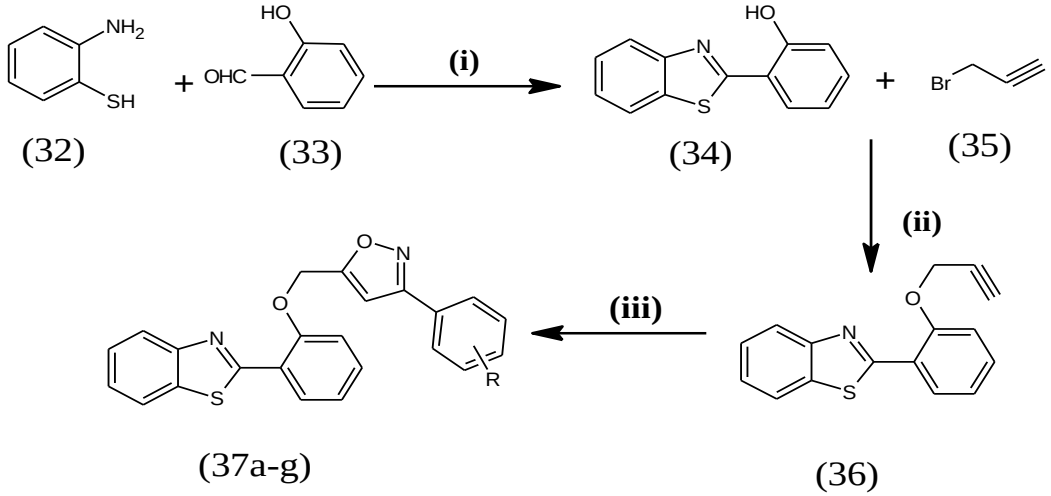


Fig. 6: Synthesis of isoxazole tagged 2H-chromen derivates

Structural modifications on benzothiazole moiety lead the way to design a number of isoxazole linked 2-phenyl benzothiazole by Kumbhare et al., The synthesis was carried out from the compounds thiophenol **(32)** and 2-hydroxy benzaldehyde **(33)** to yield 2-(2'-hydroxy phenyl) benzothiazole compound **(34)** coupled with propargyl bromide to give compound **(36)** which were treated with oximes and aromatic /aliphatic azides generated respective isoxazoles **(37a-g).**

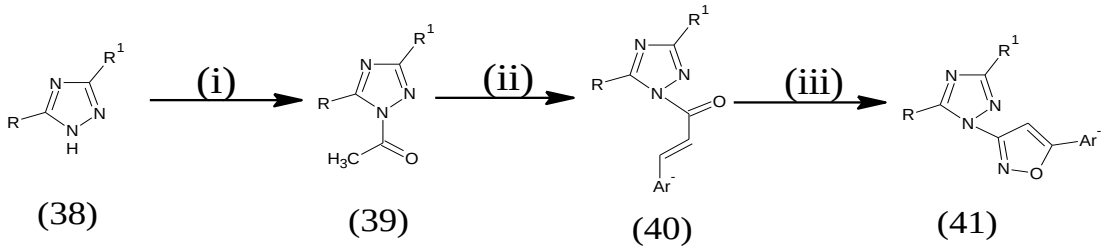


37a R= 4-CH_3
37b R= 4-OCH_3
37c R= 2-F
37d R= 4-Cl
37e R= 4-Br
37f R= 4-OCF_3
37g R= 3,4,5-OCH_3

(i) H_2O_2/CAN,heat,50^oC
(ii)Acetone,K_2CO_3,reflux,2 hrs
(iii)Aq NaOCl(9-12%),DCM,Et3N,oxime,rt,24hrs,65-75%

Fig. 7: Synthesis of isoxazole limked 2-phenyl benzthiazole derivates

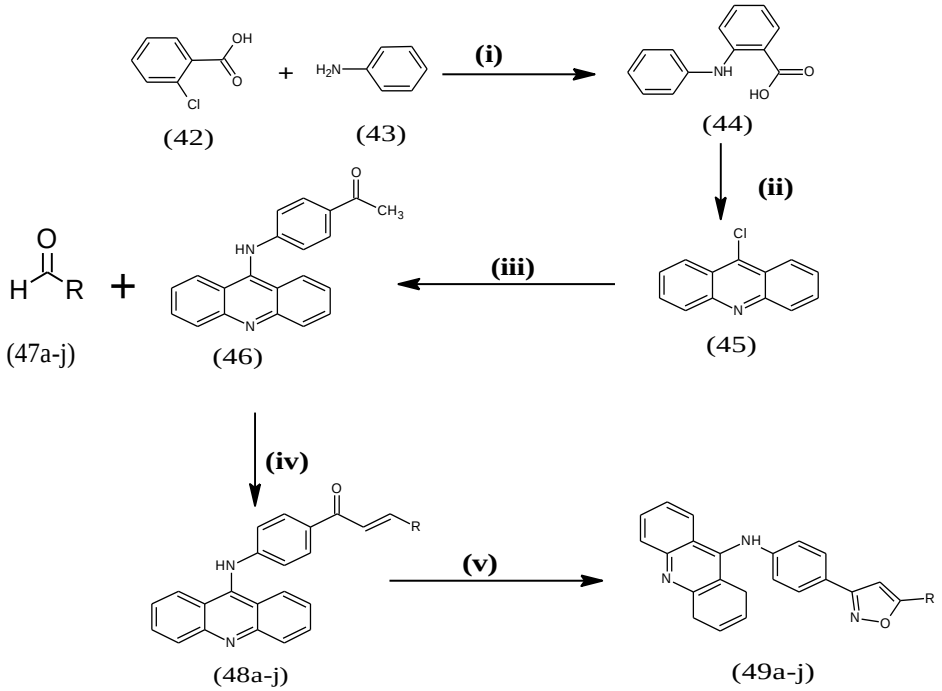
A new class of isoxazole derivatives containing 1,2,4-triazole moiety were synthesized by Khanage et al., as illustrated in figure 8. Reacting the suitable 1,2,4-triazoles **(38)** with acetic anhydride and Conc.H_2SO_4 offered the acetylated compounds **(39)**.These were simply turned to the corresponding chalcones **(40)** by reacting them with the substituted aromatic aldehydes. Cyclisation of the chalcones with hydroxyl amine HCl in basic medium imparted the desired isoxazole derivatives **(41).**



(i) $(CH_3CO)_2O$ (ii) ArCHO (iii) $NH_2OH.HCl$

Fig. 8: Synthesis of isoxazole derivates containing 1, 2, 4-triazole moiety

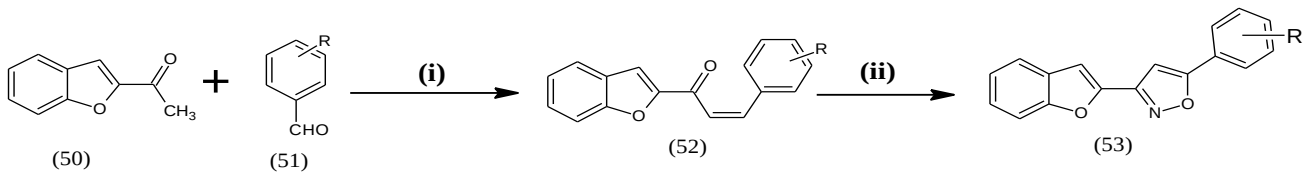
A convenient synthesis of novel isoxazole substituted 9-anilino acridine derivatives **(49a-j)** was reported by Kalirajan et al.,They have synthesized ten derivatives of isoxazole containing heterocyclic compound acridine exhibit synergetic effect compared to the individual pharmacophores.Intermediates chalcones **(48a-j)** were synthesized by using several Claisen condensation of 1,(4 – (acridin-9-yl amino)phenyl) ethanone **(46)** which are treated with substituted aromatic aldehyde **(47a-j)** in the presence of 10% NaOH by using ethanol as solvent. Cyclisation of chalcones with hydroxyl amine HCl results in to respective isoxazole derivatives.



(i) CuO,Anhyd K_2CO_3,heat (ii)$POCl_3$ (iii) 4-amino acetophenone,heat,2-BuOH
(iv)EtOH,10% NaOH, (V)$NH_2OH.HCl$,CH_3COONa,CH_3COOH,heat

Fig. 9: Synthesis of isoxazole substituted 9-anilino acridine derivates

In a strive to synthesize a series of novel isoxazole derivatives incorporating benzofuran moiety.Chetan et al., conventionally reacted benzofuran chalcones with hydroxyl amine HCl in presence of sodium acetate in ethanol.

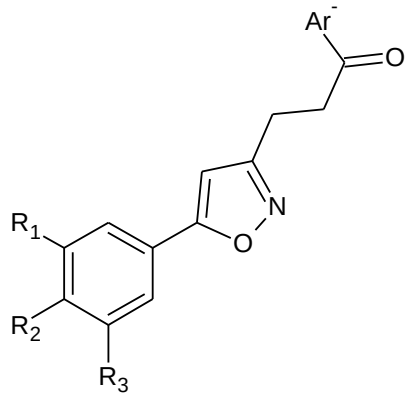


(i) Ethanol(95%),KOH(10%) (ii) $NH_2OH.HCl$,CH_3COONa,Ethanol

Fig. 10: Synthesis of isoxazole incorporating benzofuran moiety

3. ANTICANCER ACTIVITY

Compounds **(54a-54m)** were evaluated for their anti-cancer activity in selected human cancer cell lines like prostate cancer (DU145), breast cancer (MDA MB-231,MCF-7) and non-small cell lung cancer cell lines (A549) by using sulforhodamine B(SRB) method using trimethoxy chalcone(TMC) as positive control. Comparison of the IC_{50} values of the compounds revealed that **54a, 54b, 54e, 54i, 54j** and **54k** exhibited potent cytotoxic activity against prostate DU-145 cancer cell line.

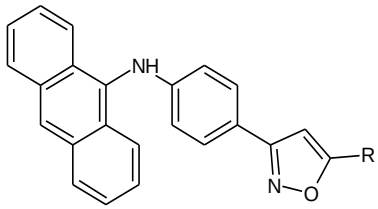


Hybrid isoxazole-chalcone derivatives (54a-m)

54a, $R_1=R_2=R_3=OCH_3$; Ar=3, 4, 5-trimethoxy phenyl
54b, $R_1=R_2=R_3=OCH_3$; Ar=3, 4-dimethoxy phenyl
54c, $R_1=R_2=R_3=OCH_3$; Ar=4-methoxy phenyl
54d, $R_1=R_2=R_3=OCH_3$; Ar=4-fluoro phenyl
54e, R_1=H, $R2=R_3=OCH_3$; Ar=3, 4, 5-trimethoxy phenyl
54f, R_1=H, $R2=R_3=OCH_3$; Ar=3, 4-dimethoxy phenyl
54g, R_1=H, $R2=R_3=OCH_3$; Ar=4-methoxy phenyl
54h, R_1=H, $R2=R_3=OCH_3$; Ar=4-fluoro phenyl
54i, R_1=H, $R2=OCH_3$, R3=H; Ar=3, 4, 5-trimethoxy phenyl
54j, R_1=H, $R2=OCH_3$, R3=H; Ar=3, 4-dimethoxy phenyl
54k, R_1=H, $R2=OCH_3$, R3=H; Ar=4-methoxy phenyl
54l, R_1=H, $R2=OCH_3$, R3=H; Ar=4-fluoro phenyl
54m, R_1=H, R2=F, R3=H; Ar=3, 4, 5-trimethoxy phenyl

Fig. 11: Hybrid isoxazole-chalcone derivates (54a-m)

The synthesized final compounds **(55a-55j)** were subjected to short term study for in vitro cytotoxic activity against Dalton Lymphoma Ascites (DLA) cells. All the isoxazole substituted derivatives have a promising role to play as anti-cancer agents and **55i** (Cyto50=311.75µg/ml) showed more potent cytotoxic activity.



Isoxazole-substituted 9-anilino acridine derivatives(55a-55j)

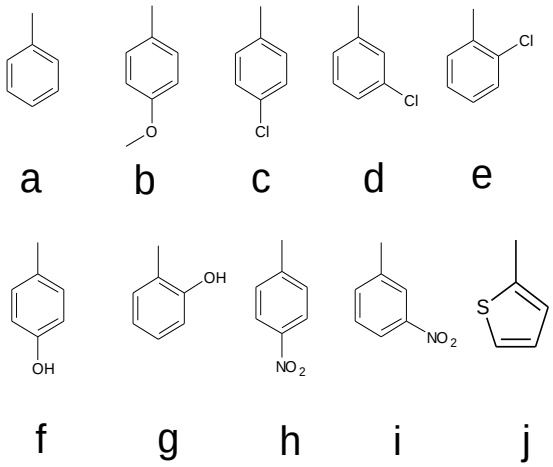
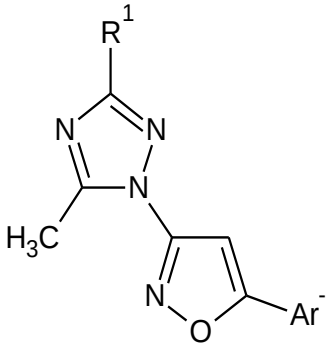


Fig. 12: Isoxazole substituted 9-anilino aceidine derivates (55a-55j)

Using the SRB method, compounds **(56a-h)** were evaluated at single concentration of 10^{-5}M towards the panel of approximately 60 cancer cell lines derived from nine different cancer types such as leukemia, lung, colon, melanoma, ovarian, CNS, renal, prostate and breast cancers. The most efficient anticancer compound **(56e)** was found to be active with selective influence on leukemia cancer cell lines with a growth % of 71.72.

R = R^1 = Phenyl ring



Isoxazole derivatives containing 1,2,4 triazole moiety (56a-h)

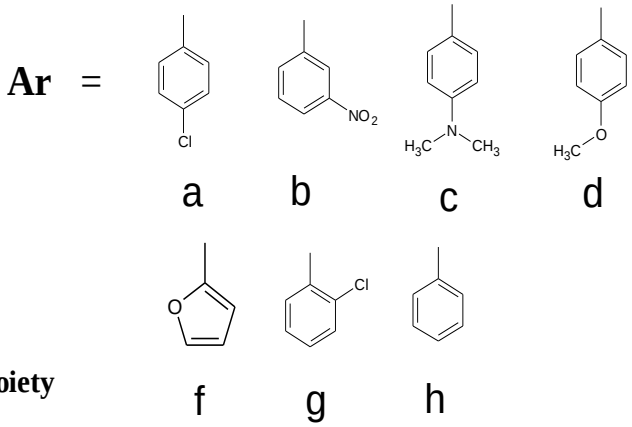
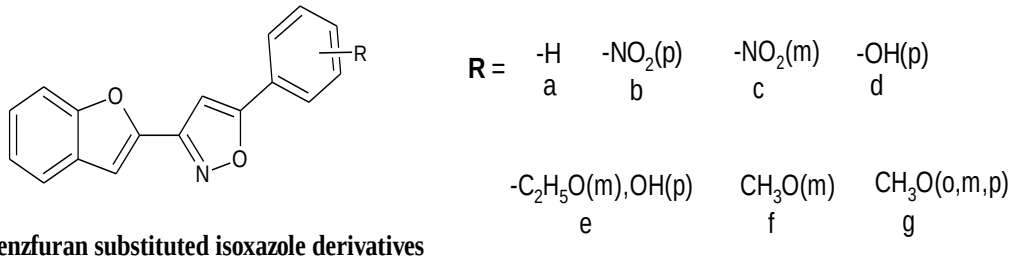


Fig. 13: Isoxazole derivates containing 1, 2, 4 triazole moiety (56-h)

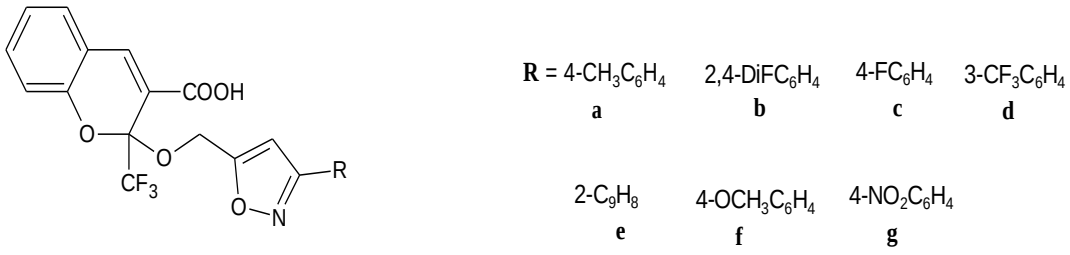
Evaluation of cytotoxic activity of compounds **(57a-g)** against HeLa cell lines of two fold dilution of seven concentration ranging from 1000-15.5µg/ml was carried out using MTT assay. Among all the compounds tested, **57d** (CTC_{50}=376.25 µg/ml) shows potent cytotoxic effect, while compound **57e** (CTC_{50}=762.28 µg/ml) shows moderate cytotoxic effect on HeLa cells.



Benzfuran substituted isoxazole derivatives (57a-g)

Fig. 14: Benzfuran substituted isoxazole derivates (57-a-)

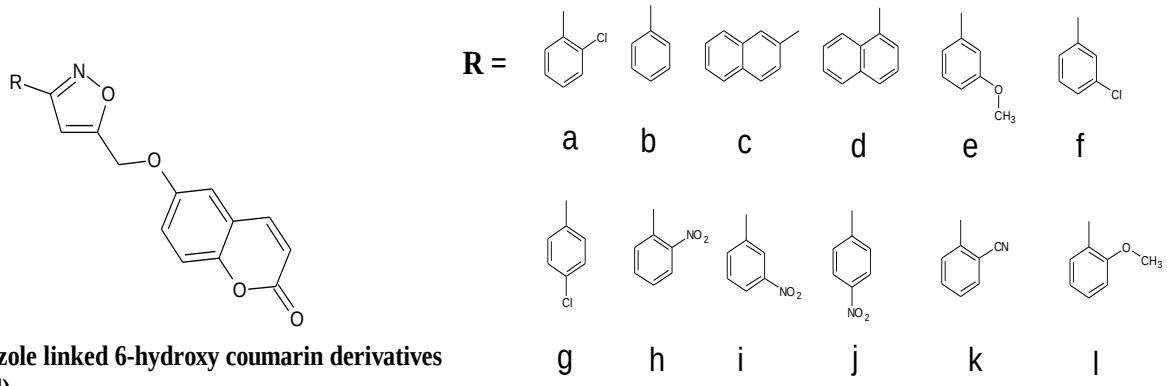
Following the MTT assay, compounds **(58a-g)** were screened against four human cancer cell lines namely Lung cancer A549,Breast cancer MCF7, Prostate cancer DU145,HeLa-cervical cancer.5-Fluorouracil was used as the positive control.**58a** and **58f** showed moderate activity at <50µM concentration.



Isoxazole functionalized 2H-chroman derivatives (58a-g)

Fig. 15: Isoxazole functionalized 2H-chroman derivates

All the derivatives of isoxazole linked 6-hydroxy coumarin **(59a-l)** were subjected to MTT cytotoxicity screening against a panel of 5 different human cancer cell lines viz. Prostate (PC-3), colon (HCT-116 and COLO-205), Leukemia (HL-60) and Lung (A-549) to check their cytotoxic potential.Compounds **59h** and **59k** showed the best activity with IC50 of 8.2 and 13.6µM against PC-3 cancer cell lines.



Isoxazole linked 6-hydroxy coumarin derivatives (59a-l)

Fig. 16: Isoxazole linked 6-hydroxy coumarin derivates (59a-l)

4. CONCLUSION

Isoxazole is a monocyclic heteroarene with a structure consisting of 5-membered ring containing heteroatoms, oxygen and nitrogen adjacent to each other. This review presents the synthesis of hybrid molecules of isoxazole derivatives and evaluation of their anticancer activity. The structural modification of isoxazole compounds confers a synergistic effect on the tested cancer cell lines. These observations would be valuable for further development of heterocyclic linked isoxazole derivatives.

5. AKNOWLEDGEMENT

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