AMINO THIAZOLE AND IT'S VARIOUS BIOLGICAL ACTIVITIES: AN OVERVIEW

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Summary

Five membered aromatic systems having two heteroatoms at 1, 3 positions such as amino thiazoles have been studied extensively owing to their interesting pharmacological activities. This review article covers the most active amino thiazole derivatives that have shown considerable biological actions such as antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radioprotective and anti-leishmanial. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing thiadiazoles moiety that could be better agents in terms of efficacy and safety.

Key-words: Amino thiazole, SAR, Biological activities, Total synthesis.

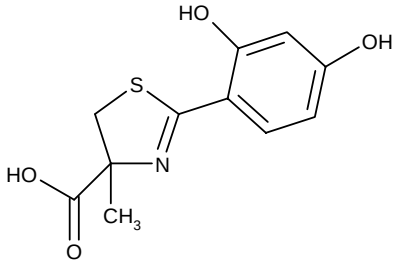
Introduction

The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research today.2-Aminothiazole is a heterocyclic amine with odor similar to pyridine, soluble in water, alcohol and ether. It is a beginning point for synthesis of many compounds including sulfur drugs, biocides, fungicides, dyes and chemical reaction accelerators. 2-Aminothiazole can be used as a candiadate for treatment of various disorders.Literature review shows that it possess wide variety of biological activities.

In treatment of β-thalassemia [1]

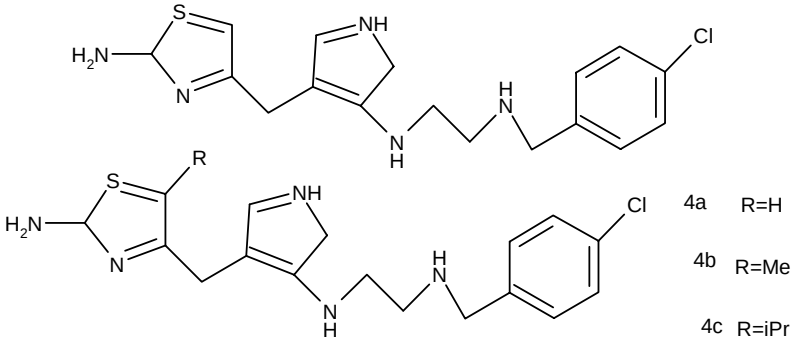
Deferitrin

Deferitrin GT-56-252 is the first drug in a class of desferrithiocin-derived hexadentate ron chelators. Genzyme Corp is developing this compound as an oral drug for the treatment of severe iron overload in people who require repeated erythrocyte transfusion for management of chronic anemia such as β-thalassemia major. In phase I clinical trials in adults with β-thalassemia, deferitrin promoted iron excretion in a dose-related manner and was well tolerated as both a liquid and capsule in fed and fasted states. There were no serious adverse events or significant laboratory abnormalities. Deferitrin may be useful as chelation monotherapy or as part of combination or doublet chelation therapy for the treatment of severe iron overload in patients with β-thalassemia major if its favorable pharmacokinetic profile, efficacy, safety and tolerability are confirmed in more extensive clinical trials.



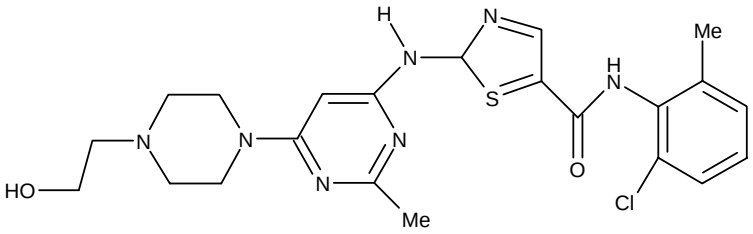
Inhibitors of neuronal nitric oxide synthase [2]

Highly potent and selective inhibitors of neuronal nitric oxide synthase nNOS possessing a 2- aminopyridine group were recently designed and synthesized in our laboratory and were shown to have significant in vivo efficacy. In this work, analogs of our lead compound possessing 2- and 4-aminothiazole rings in place of the aminopyridine were synthesized. The less basic aminothiazole rings will be less protonated at physiological pH than the aminopyridine ring, and so the molecule will carry a lower net charge.This could lead to an increased ability to cross the blood-brain barrier thereby increasing the in vivo potency of these compounds. The 2-aminothiazole-based compound was less potent than the 2-aminopyridine-based analogue. 4-Aminothiazoles were unstable in water, undergoing tautomerization and hydrolysis to give inactive thiazolones.



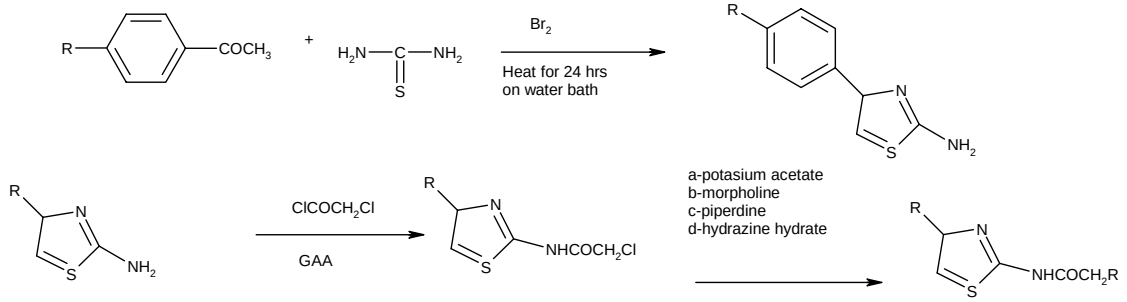
Anti-cancer activity

A new and efficient method has been developed for the synthesis of 2-amino-N--2-chloro-6- methylphenyl-thiazole-5-carboxamide. The new method involves a chemoselective α- bromination of β-ethoxyacrylamide followed by a one-pot treatment with thiourea to give the desired 2-aminothiazole-5-carboxylamide in excellent yield. Application of this new method to the efficient synthesis of the anti-cancer drug dasatinib was demonstrated.[3]



Anti microbial activity

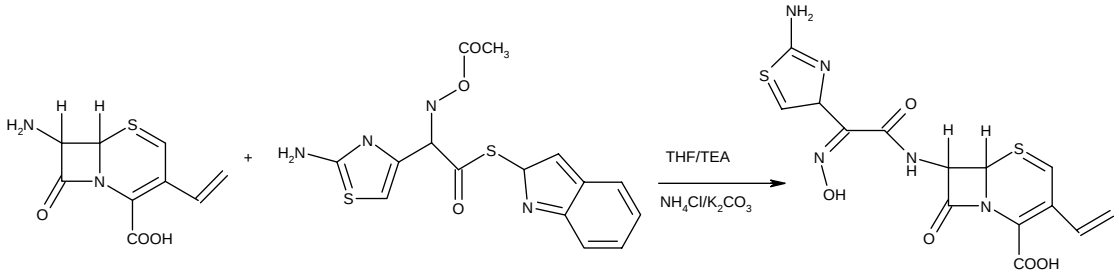
1. The present work deals with synthesis and evaluation of substituted thiazoles amino thiazoles and their derivatives of biological interest and also represents some of the salient aspect of the application of organo Sulphur compounds in particular. Thiazoles containing N=C-S moiety has been employed as antipsychotic and antibacterial. Thiazole derivative particularly amino thiazoles play vital role in pharmaceutical practice owing to their wide biological activities like fungicidal, antimicrobial, anti TB, anti cancer and anti-inflammatory. The substituted thiazoles compounds have number of characteristic pharmacological features such as Relative stability and ease of starting materials, Built in biocidal unit, Enhanced lipid solubility with hydrophilitcity, Easy metabolism of compounds.[4]



Synthesis of potential related compounds of Cefdinir

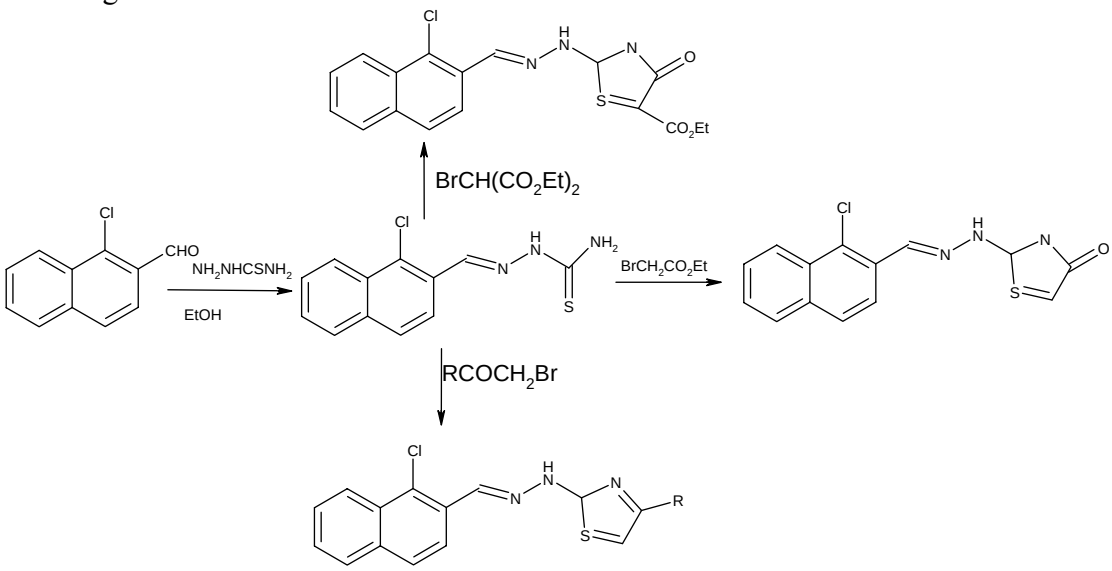
2. Cefdinir **1** is [*syn*-7- [2-2-aminothiazole-4-yl-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid]. It is a third generation cephalosporin antibacterial drug for oral administration. The most remarkable future of Cefdinir is the excellent activity against staphylococcus species. Several methods are reported in

the literature for the preparation of Cefdinir 3-7, but the related compounds were not discussed. However, the degradation kinetics of Cefdinir has been cited in the literature. The preparation of these three contaminants has been necessary for the preparation of reference compounds for the quality control of bulk drugs and drug formulations, and pathways have been developed starting from the parent Cefdinir.[5]



Synthesis and antimicrobial evaluation of some new thiazole, thiazolidinone and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde

3. The thiosemicarbazones 3 and 6 and N-arylidene cyanoacetohydrazide 12 were prepared and used as key intermediates for the synthesis of 4-thiazolidinones 4, 5, 7e9, thiazoles 10a,b and 11aed and thiazoline 13 derivatives. Treatment of 13 with a mixture of triethylorthoformate and acetic anhydride afforded thiazolo[5,4-d]pyrimidinone derivative 14. The newly synthesized compounds were characterized by IR, 1H NMR and mass spectral studies. Representative compounds of the synthesized products were tested and evaluated as antimicrobial agents.[6]

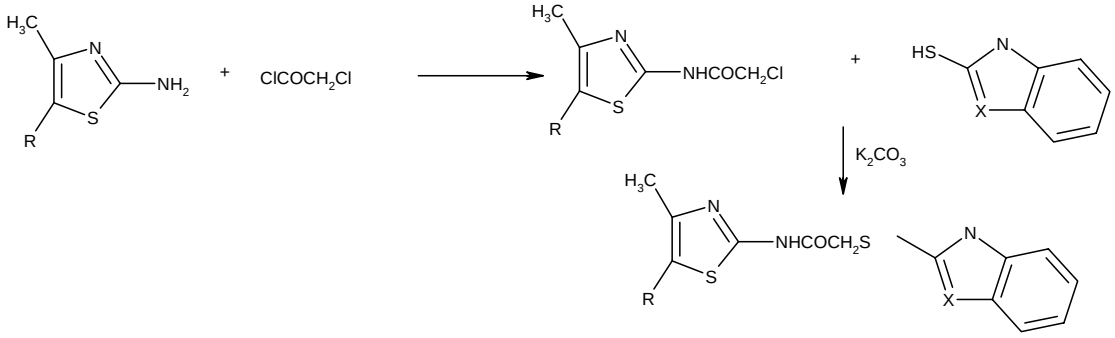


Copper II Schiff base coordination compounds of dien with heterocyclic aldehydes and 2-amino-5-methyl-thiazole: synthesis, characterization, antiproliferative and antibacterial studies. Crystal structure of CudienOOCl2

4. A new series of coordination compounds of the starting materials [CudienX2Y2] and their adducts [CudienXXY22a-5mt] where dien¼diethylenetriamine, dienXX¼Schiff bases of diethylenetriamine with 2-furaldehyde or 2-thiophene-carboxaldehyde, X¼O, S, Y¼Cl, Br, NO3 and 2a-5mt¼2-amino-5-methylthiazole were synthesized by stepwise reactions and their structures were established by C, H, N, Cu analysis, spectroscopic, magnetic and molar conductivity measurements. The isolated compounds are monomers, paramagnetic and electrolytic compounds of the type 1:1. In all cases, the pentadentate Schiff base dienXX is bonded in a tridentate fashion through the 3 N atoms. In the CudienXXY2 compounds the coordination sphere is completed by two Cl or Br or NO3 groups in a square pyramidal arrangement. The proposed structure for this type of compound was further supported by Xray diffraction analysis of the compound [CudienOOCl2]. Its basal plane consists of three Cu–N contacts [2.0172, 2.0252 and 2.0122 _A] from dienOO, and the Cl1 atom, while the Cl2 atom possesses the apical position, the relevant distances being 2.27327 _A for Cu–Cl1 and 2.60517 _A Cu–Cl2. In the CudienX2Y2 Æ 2a-5mt adducts the coordination sphere of copper is further completed by the nitrogen ring atom of the 2a-5mt, forming an octahedral configuration. The study of the biological activity of the compounds synthesized against a panel of different normal and cancer cell lines MRC5, HeLa, MCF7, HT-29, OAW42, T47D and bacteria E. coli, B. cereus, B. subtilis showed that the adducts of the type [CudienXXY22a-5mt] exhibit increased activity both in cancer cells and in bacteria, compared to the starting material of type [CudienXXY2].[7]

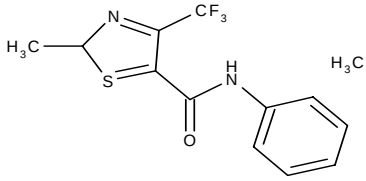
Synthesis of some 2-[benzazole-2-ylthioacetylamino]thiazole derivatives and their antimicrobial activity and toxicity

5. Some 2-[benzazole-2-ylthioacetylamino]thiazole derivatives **III** were synthesized by reacting 4-methyl-2-chloroacetylaminothiazole derivatives **I** with benzazol-2-thiole **II** in acetone in the presence of K2CO3. The chemical structures of the compounds were elucidated by 1H NMR and FAB+-MS spectral data. The prepared compounds were tested for antimicrobial activity and toxicity.[8]

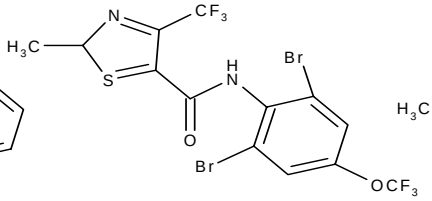


Synthesis and biological activity of novel 2-methyl-4-trifluoromethyl-thiazole-5-carboxamide derivatives

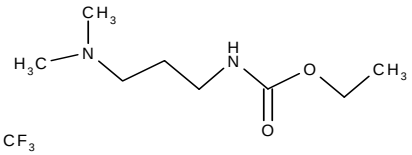
6. Nine novel 2-methyl-4-trifluoromethylthiazole-5-carboxamide derivatives were designed and synthesized utilizing ethyl 4,4,4-trifluoroacetoacetate as a starting material. Subsequently, the biological activity of the compounds was evaluated in the greenhouse. Results indicated that all of the compounds have some fungicidal and insecticidal activity but no herbicidal activity. Compound 1 has fungicidal activity with 90% control of tomato late blight at 375 g ai/ha, while two compounds 2F and 2H show insecticidal activity with 80 and 100% control, respectively, against potato leafhopper at 600 g ai/ha.[9]



metasulfovax



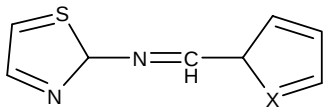
thifuzamide



propamocarb

Synthesis, Characterization And Biological Properties Of Tridentate Nno, Nns And Nnn Donor Thiazole-Derived Furanyl, Thiophenyl And Pyrrolyl Schiff Bases And Their CoLl, CuLl, NiLl And ZnLl Metal Chelates

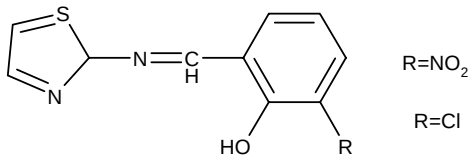
7. 2-Aminothiazole undergoes condensation reactions with furane-, thiophene- and pyrrole-2-carboxylaldehyde to give tridentate NNO, NNS and NNN Schiff bases respectively. These tridentate Schiff bases formed complexes of the type [ML2]Xz where [M Coll, CuII, NiII or ZnII, L N-2-furanylmethylene-2-Aminothiazole tL,N-2-thiophenylmethylene-2-aminothiazole L, N-2-pyrrolylmethylene-2- aminothiazole L and X CI.The screening results of these compounds indicated them to possess excellent antibacterial activity against tested pathogenic bacterial organisms e.g., Escherichia coli, Staphylococcus aureous and Pseudomonas aeruginosa. [10]



Biologically active transition metal chelates of nill, Cull and znll with 2-aminothiazole-derived schiffbases: Their synthesis, characterization and the role Of anions NO, SO4', CO4-and CHCO2- on their antibacterial properties

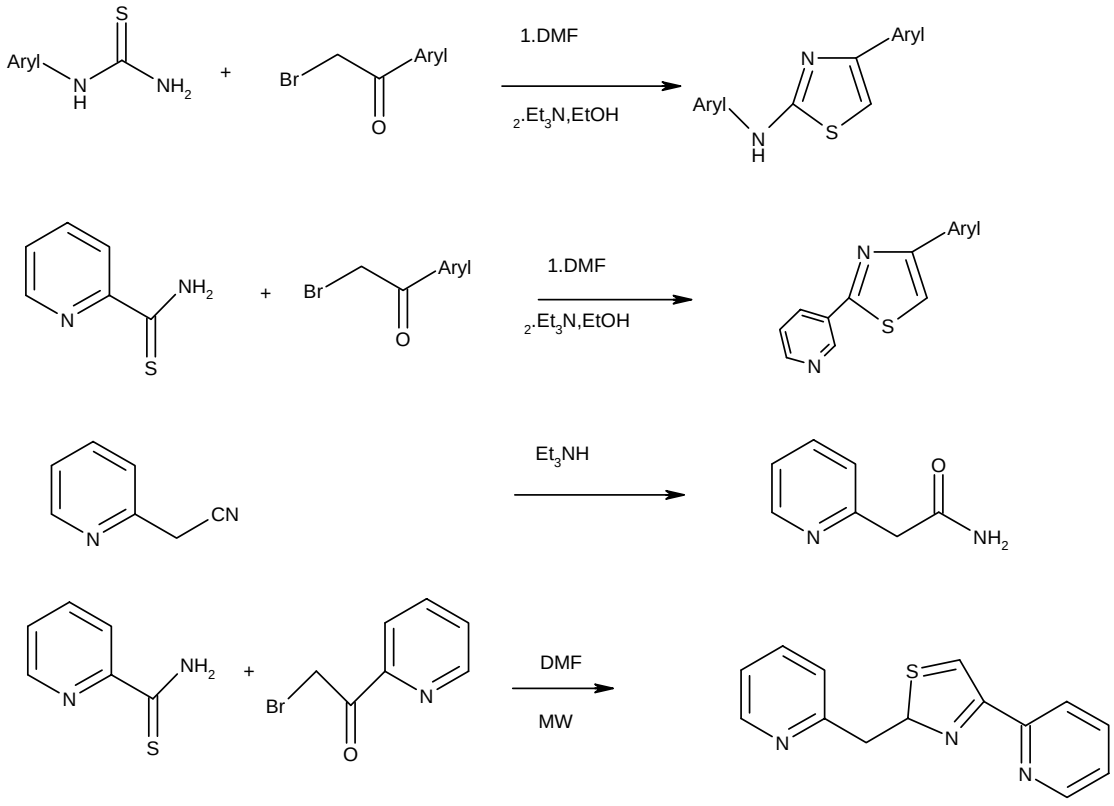
8. Biologically active nickelll, copperll and zincll chelates with thiazole-derived nitro- and chlorosalicylaldehyde Schiff-bases having the same metal ion but different anions, e.g. nitrate, sulfate, oxalate and acetate have been synthesized and characterized on the basis of their physical, spectral and analytical data. In order to evaluate the possible participating role of anions on the antibacterial

properties, these ligands and their synthesized metal chelates with various anions have been screened against bacterial species Escherichia co/i, Pseudomonas aeruginosa and Staphylococcus aureus.[11]



KCa2 channel blockers

An initial SAR study on a series of apamin-displacing 2-aminothiazole KCa2 channel blockers is described. Potent inhibitors such as N-4-methylpyridin-2-yl-4-pyridin-2-ylthiazol-2-amine are disclosed, and for select members of the series, the relationship between the observed activity in a thallium flux, a binding and a whole-cell electrophysiology assay is presented.[12]



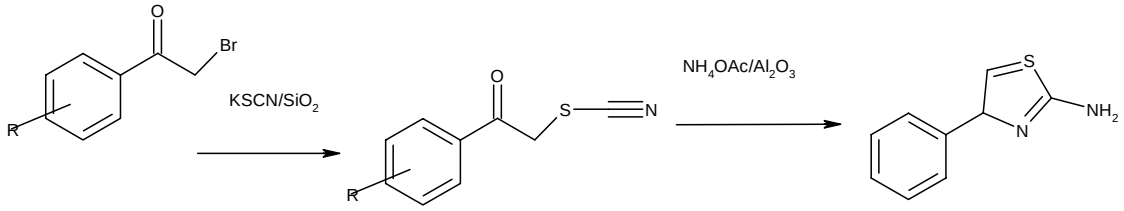
Anti ulcerogenic activity

Mutual prodrug of indomethacin with 5-phenyl2-aminothiazole was synthesized by coupling aminothiazole with indomethacin using N,N'carbonyldiimidazole. The structure was confirmed by elemental analysis, UV, IR and NMR spectroscopy. *In-vitro* kinetic

studies was performed using UV spectroscopy. The *in-vivo* hydrolysis studies was performed by HPLC Inertsil, 250x4.6mm 5µ C18 column Cecil liquid chromatograph methanol: orthophosphoric acid: Water 70:0.5:29.5 used as mobile phase. Therapeutic efficacy of the prodrug were evaluated using writhing and hotplate methods on albino mice for its expected analgesic activity and anti-inflammatory activity was evaluated using carrageenan induced paw oedema method in wistar rat model. Finally the synthesized prodrug was subjected for determination of ulcerogenic potential using ulceration count method.[13]

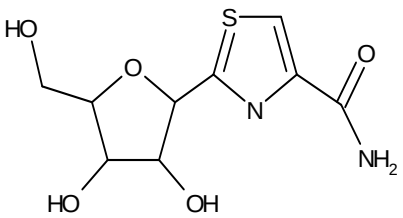
Adenosine A3 receptor antagonists.

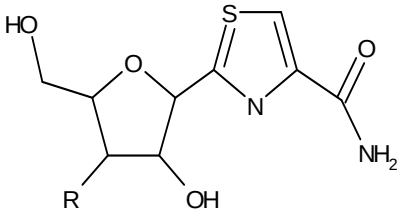
4-4-Methoxyphenyl-2-aminothiazole and 3-4-methoxyphenyl-5-aminothiadiazole derivatives have been synthesized and evaluated as selective antagonists for human adenosineA3 receptors.Amethoxy group in the 4-position of the phenyl ring andN-acetyl or propionyl substitutions of the aminothiazole and aminothiadiazole templates displayed great increases of binding affinity and selectivity for human adenosine A3 receptors. The most potent A3 antagonist of the present series, N-[3-4-methoxy-phenyl-[1,2,4]thiadiazol-5-yl]-acetamide exhibiting aKi value of 0.79 nMat human adenosineA3 receptors, showed antagonistic property in a functional assay of cAMP biosynthesis involved in one of the signal transduction pathways of adenosine A3 receptors.Molecular modeling study of conformation search and receptor docking experiments to investigate the dramatic differences of binding affinities between two regioisomers of thiadiazole analogues, suggested possible binding mechanisms in the binding pockets of adenosine receptors.[14]



Antitumour activity

A new tiazofurin analogue, 2-3-amino-3-deoxy-b-D-xylofuranosylthiazole-4-carboxamide 3, was synthesized starting from D-glucose and evaluated for its in vitro antiproliferative activity against a panel of human tumour cell lines. Compound 3 exhibited the most powerful cytotoxicity against K562 cells, being approximately 100-fold more potent than tiazofurin. This analogue was also active against Jurkat, HT-29 and HeLa malignant cells, with respective IC50 values being ca. 2-, 27- and 17-fold lower than those observed for tiazofurin. Remarkably, compound 3 did not exhibit any significant cytotoxicity towards normal foetal lung MRC-5 cell line.[15]



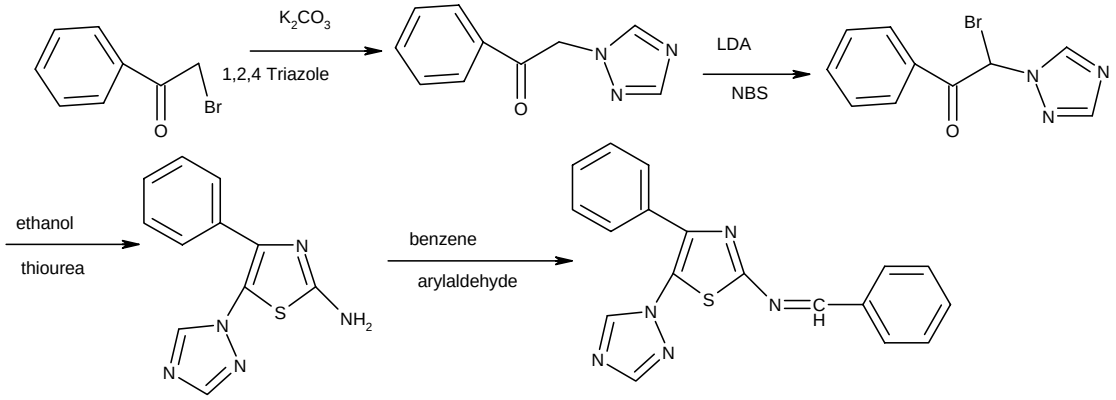


R=NHAc

R=NH_2

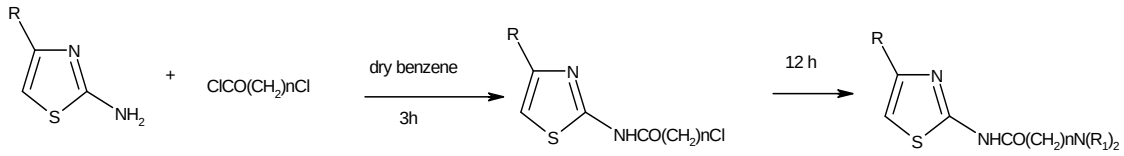
Antifungal activity

A series of ferrocene-containing N-substituted benzylidene- 4-ferrocenyl-5-1H-1,2,4-triazol-1-yl-1,3-thiazol-2-amine derivatives were synthesized and their structures were verified by elemental analysis, 1H NMR and X-ray diffraction analysis. These novel 2-thiazoleimine derivatives were screened for their biological activities. The screening data revealed that compounds 5 show some antifungal activities and plant growth regulatory activity. Further structure modification and optimization of these ferrocene-containing thiazole derivatives are necessary.[16]



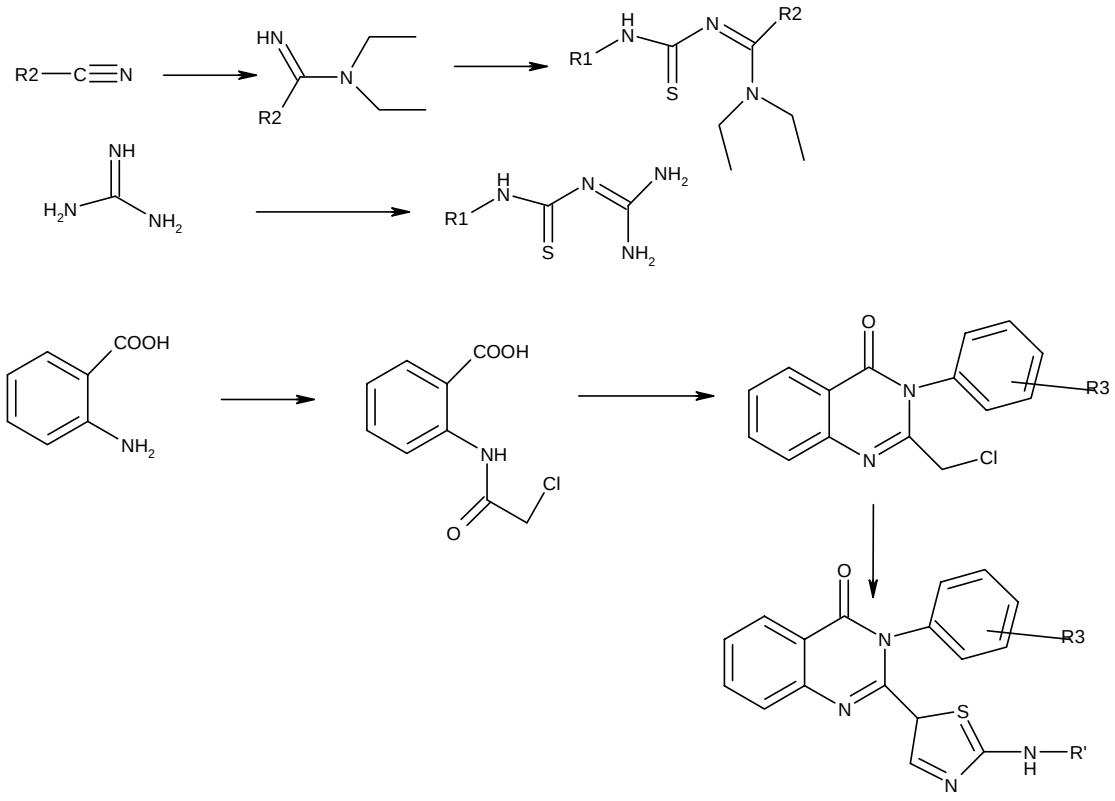
Anti-inflammatory activity

1. 4,5-disubstituted-thizolyl amides, derivatives of 4-hydroxy-piperidine and of 4-N-methyl piperazine, were synthesized and tested as anti-inflammatory agents. Log P values were theoretically calculated and experimentally determined. These compounds were tested for antioxidant activity, as hydroxyl radical scavengers and for their ability to interact with stable 1,1-diphenyl-2-picryl hydrazyl free radical DPPH. The effect of the synthesized compounds on inflammation, using the carrageenin induced mice paw edema model was studied. Both anti-inflammatory and antioxidant activities depended on some structural characteristics of the synthesized compounds.[17]



Design, synthesis and characterization of novel 2-2,4-disubstituted-thiazole-5- yl-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF-kB and AP-1 mediated transcription activation and as potential anti-inflammatory agents

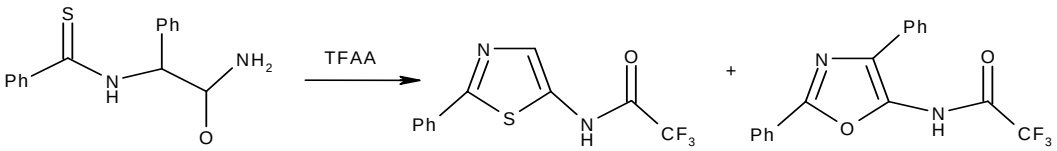
2. A series of 2-2,4-disubstituted-thiazole-5-yl-3-aryl-3H-quinazoline-4-one derivatives were designed and synthesized. Synthesized molecules were further evaluated for their inhibitory activity towards transcription factors NF-kB and AP-1 mediated transcriptional activation in a cell line based in vitro assay as well as for their anti-inflammatory activity in in vivo model of acute inflammation. This series provides us with selective and dual inhibitors of NF-kB and AP-1 mediated transcriptional activation which also exhibit significant efficacy in in vivo model of inflammation. Two of the compounds 9m and 9o turned out to be the most promising dual inhibitors of NF-kB and AP-1 mediated transcriptional activation with an IC50 of 3.3 mM for both. 9n IC50¼ 5.5 mM and 9p IC50 ¼ 5.5 mM emerged as selective inhibitors of NF-kB mediated transcriptional activation and 9c IC50¼ 5.5 mM and 9d IC50¼ 5.5 mM were found to be more selective inhibitor of AP-1 mediated transcriptional activity. Though the relationship between the activities shown by these compounds in in vivo and in vitro model is still to be established, these results suggest the suitability of the designed molecular framework as a potential anti-inflammatory molecular framework which also exhibits the inhibitory activity towards NF-kB and AP-1 mediated transcriptional activation. This will be worth studying further to explore its complete potential particularly in chronic inflammatory conditions. The structure activity relationship SAR of this series has been discussed herein.[18]



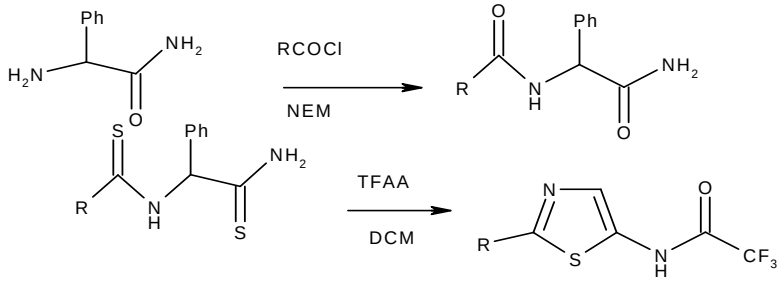
In synthesis

Synthesis of 5-aminothiazoles as building blocks for library synthesis

1. A convenient route to 4-phenyl-5-aminothiazoles is described, which offers control over substitution at the 2-position. 2-N-Acylglycinamides were dithionated and a subsequent TFAA-mediated cyclisation step was followed by removal of the 5-N-trifluoroacetyl group providing the free amines. Though applicable generally the method was found to be most effective when introducing aromatic substituents at the 2-position, whereupon moderate overall yields of the 5-amino compounds were obtained.[19]



Scheme:No regeoselectivity was seen in the TFAA modified cyclisation

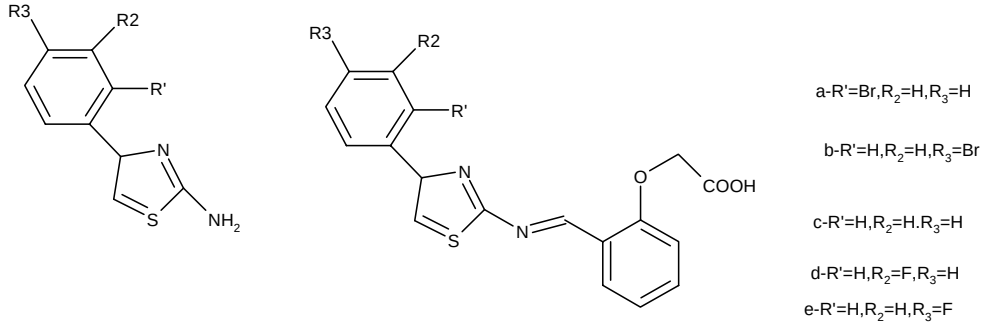


Synthesis of New Hetarylazoindole Dyes from Some 2-Aminothiazole Derivatives

2. A new series of heterocyclic disperse dyes were prepared by diazotization of some 2-aminothiazole derivatives and subsequent coupling with indole compounds. The dyes were characterized by UV-Vis, FT-IR,1H NMR, and mass spectra LC–MS. Solvent effects on their visible absorption spectra were estimated. The color of the dyes is discussed with respect to the substituent therein. The effects of acids and bases on the visible absorption maxima of the dyes are also reported. Replacement of methyl group in the 4-position of the thiazole ring by phenyl group leads to red shift of the absorption maximum due to π-electron-donating properties of the phenyl group, while weak electron-withdrawing chlorine or bromine atom in the *para*-position of the phenyl group in the 2-amino-4-phenylthiazole fragment induce a small blue shift relative to 2-amino-4-phenylthiazole derivatives. Introduction of an electron-withdrawing 4-nitrophenylsulfonyl group into the thiazole ring produces bathochromic shift of the absorption maximum in all solvents.[20]
3.

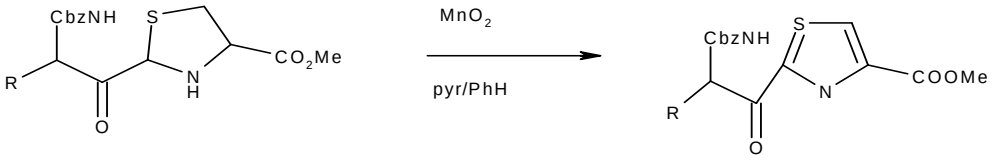
Synthesis and Spectroscopic Studies of New Schiff Bases

4. Five novel Schiff bases have been prepared from *o*-formylphenoxyacetic acid and a series of Aminothiazole to form a number of potentially biologically active compounds.[21]



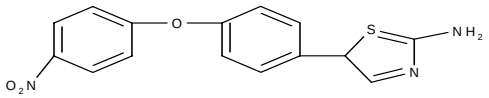
Synthesis of amino acid-derived thiazoles from enantiopure *N*-protected -amino glyoxals

5. Several novel thiazoles with side chains derived from natural amino acids and a dipeptide have been synthesized from *N*-protected _-amino glyoxals and cysteine.[22]



Synthesis and characterization of novel polyimides derived from 2-amino-5-[4-40-aminophenoxy phenyl]-thiazole with some of dianhydride monomers

6. A new kind of aromatic unsymmetrical diamine monomer containing thiazole ring, 2-amino-5-[4-40-aminophenoxyphenyl]-thiazole APPT, was synthesized. A series of novel polyimides were prepared by polycondensation of APPT with various aromatic dianhydrides via one-step process. The resulting polyimides held inherent viscosities of 0.40e0.71 dL/g and were easily dissolved in strong dipolar solvents. Meanwhile, strong and flexible polyimide films were obtained, which had thermal stability with the glass transition temperatures Tg of 268.2e328.8 _C in nitrogen, the temperature at 5% weight loss of 452e507 _C in nitrogen and 422e458 _C in air, and the residue at 800 _C of 54.18e63.33% in nitrogen, as well as exhibited outstanding mechanical properties with the tensile strengths of 105.4e125.3 MPa, elongations at breakage of 6e13%. These films also held dielectric constants of 3.01e3.18 10 MHz and showed predominantly amorphous revealed by wide-angle X-ray diffraction measurements.[23]



Conclusion

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by 2-amino thiazole derivatives. The biological profiles of these new generations of 2-amino thiazole would represent a fruitful matrix for further development of better medicinal agents.

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