Research Paper Chemistry

The Utility of Disubstituted Imidazole-2-Thione for The Synthesis of o-fused Polynuclear Heterocyclic Derivatives with Biological Interest

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ABSTRACT

Disubstituted imidazole-2-thione are ambident compounds containing a thioureide moiety. The chemistry of imidazole-2-thione is of constant interest owing to the occurrence of this ring system in various biologically important compounds.This article covers the method of preparing disubstituted imidazole-2-thione, it also includes their reactions in the past years, some of which have been applied to the synthesis of biologically important compounds.

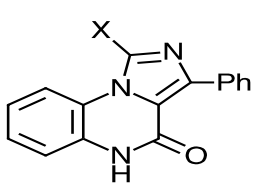
KEYWORDS Disubstituted Imidazole-2-Thione, imidazole-2-thione,pharmacological properties , bioactivities.

Introduction

Various derivatives of imidazole-2-thione have attracted widespread attention owing to their diverse pharmacological properties and bioactivities[1-3].

The oxidation of ascorbic acid to dehydroascorbic acid was accelerated by metal ions such as copper. This stimulation of ascorbate oxidation was inhibited by the addition of 2-imidazolethiones and is proposed to complex copper through their free SH groups.Copper (I) complexes of tri(o-toly)phosphine and heterocyclic thiones ligands are reported to possess antifungal activity , 1,3-disubstituted-imidazole-2-thione showed an activity against HIV-1 comparable to the activity of Nevirapine[4].

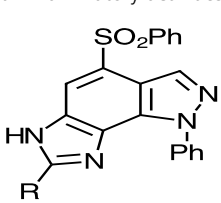
N-substituted-1-amino-2,3-dihydro-1H-imidazol-2-thiones-N-nucleosides and S-glycosides have also been prepared and tested against HIV-1 and HIV-2 induced cytopathya in human MT-4 lymphocyte cells[5].1,3-Disubstituted imidazole-2-thione are a class of versatile catalysts Furthermore, imidazole-2-thiones are light-sensitive photographic and high-speed photothermographic materials[6]. Fused azole heterocycles with bridgehead nitrogen have received considerable attention as a result of their various biological effects. Imidazo [1,5-a] quinoxalines are used in synthesis of pharmacological active compounds as agonists and antagonists of the receptor of GABA/diazepine, inhibitors of GAMP and cGMP phosphodiesterases, agonists of receptors of A_1 and A_{2a}adenosines[7].



X=SH , OH , Ph

Imidazo [1,5-a] quinoxaline derivatives

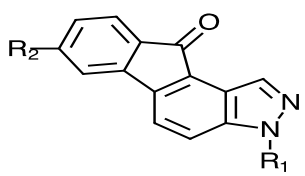
Tricyclic heteroaromatic systems of imidazole containing the annulated indazole fragment have useful biological activities , there compounds can be used as drugs with antitumor, anti-inflammatory activities[8].



R=H , CH_3 ,CF_3

1-Phenyl-4-phenylsulfonyl-1,6-dihydroimidazo[4,5-g]indazole

Fluoreno [1,2-d] imidazol-10-ones are bioactive compounds which are widely used as antiviral[9,10] and anticancer[11].They have mainly been considered as an important unit in polymer chemistry[12-14].



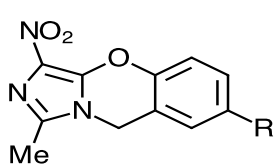
R_1=Et , R_2=H

R_1= Pr , R_2=Cl

R_1= Bu , R_2=OMe

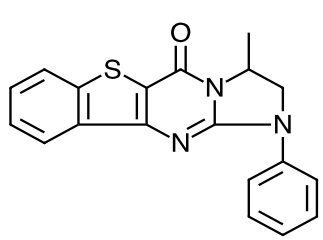
Fluoreno [1,2-d] imidazol-10-one

Condensed imidazo [5,1-b][1,3] benzoxazine high biological activity[15,16].Thienopyrimidine derivatives are of interest as possible antiviral agents, antibacterial, antifungal, antiallergic and antinflammatory activities[17,18].



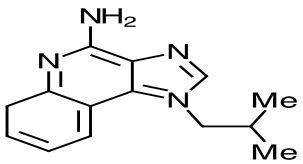
R=Br , NO_2

Imidazo [5,1-b][1,3] benzoxazine



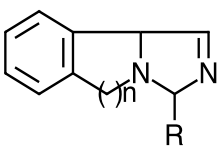
3-Methyl-1-phenyl benzothio [3,2-d]-imidazo[1,2-a]pyrimidine-2,5(1H,3H)- dione

Imiquimod is the first antileishmanial chemotherapeutic compound[19,20], which exhibits wide-spectrum antiviral activity, used to treated genital and anal Warts and immune response modifier[21].



1-(2-methyl propyl)-1H-imidazo[4,5-c]quinolin-4-amine (Imiquimod)

Imidazo[5,1-a] isoindol is heterocyclic systems shown to have anti-anxiety, asthmatic, tumour, bacterial and inflammatory activity[22,33].

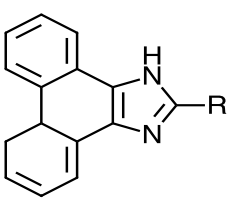


R=H , n=1-3

R=Ph ,n=1-3

Imidazo[5,1-a] isoindol

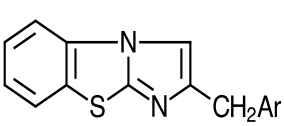
Phenanthroimidazole derivatives are predrugs compounds[24], cytotoxic effect[25,26],analgesicactivity[27,28],electroluminescent material and two-photon absorbtion (TPA) materials[29-31], which converted fluorescence techniques for laser spectroscopy, laser processing and noninvasive monitoring of tissues.



R=$C_6H_2(OCH_3)_3$, C_6H_4OH , C_6H_4X , $C_6H_4OCH_3$, C_6H_5 , $C_{17}H_{35}$, CH_3

2-Substituted-1H-Phenanthro[9,10-d]imidazole

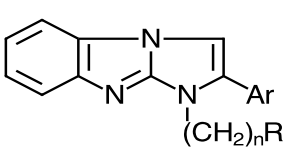
Imidazobenzothiazole derivatives are common substructures of synthetic molecules displaying important medicinal activity[32]. Their core ring system is present in numerous carditonic[33] and immunosuppressive drugs[34].



Ar =o-$NO_2C_6H_4$, m-$NO_2C_6H_4$, p-$NO_2C_6H_4$

2-Substituted imidazo[2,1-b][1,3]benzothiazole

Imidazo [1,2-a] benzimidazole is a heteroaromatic system that can adopt two tautomeric forms. Such isomers will exhibit higher biological activity[35].

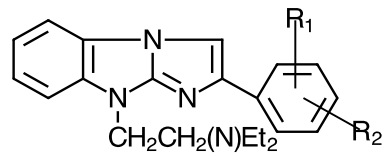


Ar =3-$OCH_3C_6H_4$, 4-OHC_6H_4

R = N(CH2)5 , N(CH2CH2)O

Imidazo [1,2-a] benzimidazole

Imidazo[1,2-a] benzimidazole derivatives used for the treatment of various pathotogical processes involving lipid peroxidation, spasmolytic, antiaggregant, hemorheological, anticalmodulin antiulcer and hypotensive activity[36].

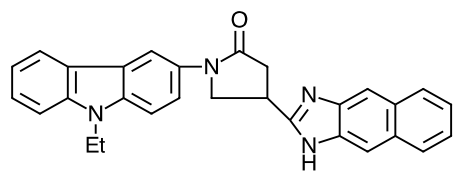


R_1 = 4-OH ,3-OH , 3,4-$(OH)_2$, R_2 =H

R_1 = H, R_2 =2,4-$(OH)_2$, 2,5-$(OH)_2$

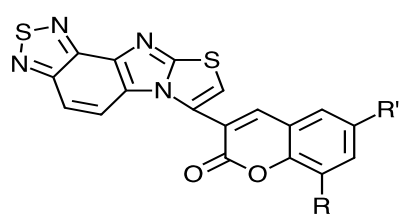
9-Dialkylaminoethyi-2-oxy(dioxy)-phenyl imidazo[1,2-a] benzimidazole

Naphtho[2,3-d] imidazole derivative exhibit hole-transporting properties used in electrography[37].



1-(9-Ethyl-9H-carbazol-3-yl)-4-(1H-naphtho[2,3-d]imidazole-2-yl)-2-pyrolidinone

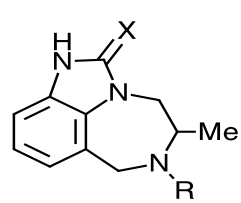
Combination of benzimidazothiazole system and coumarin ring was though to be of interest in view of the fact that pyrone ring is known to be hydrolyzed in animals, resulting in the formation of corboxyl group. The resulting compounds would be isosteric with thiazole-4-acetic acid, which are known for their inflammation – inhibiting effect[38].



R=R' =H,
R=H , R' =Br
R=R'= Br
R=Cl , R'=H
R=R'=Cl
R=H , R'=NO_2

3-(2,8-dithia 1,3,5b, 9-tetraaza cyclopenta(b)-as-indacen-6-yl)chromen-2-ones

Tetrahydroimidazodiazepinone derivatives are drug-receptor interaction with their receptor which measurement of strength of hydrogen bond formed between drug and receptor[39].



X= O ,S

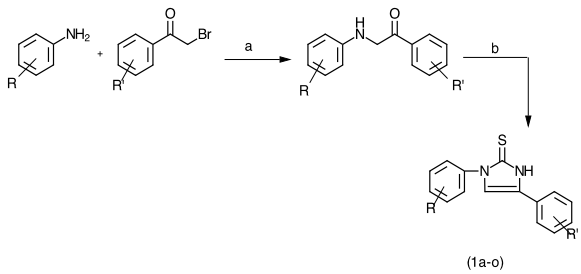
Tetrahydroimidazodiazepinone

2. Synthesis of Disubstituted imidazole-2-thione:

2.1. 1,4-Disubstituted imidazole-2-thione 1

Thus upon reaction between N-aryl phenacylamines and ammonium thiocyanate in boiling 10% hydrochloric acid, compounds 1a-o were obtained in 64-86% yields.Synthesized compounds were evaluated in vitro for antitumor activity

against the human cancer cell panel. Compounds bearing 3,4,5-trimethoxy phenylring linked to either N-1 or C-4 position of imidazole core demonstrated an interesting profile of cytotoxicity with preferential activity against leukemic cell lines. Basic nitrogen atoms of the imidazole ring may lead to compounds with decreased lipophilicity that canbe formulated into water-soluble salts to give improved pharmacokinetic properties[40](scheme 1).



(1a-o)

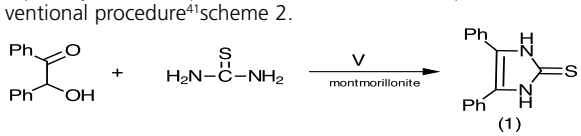
R = 3,4,5-$(MeO)_3$; R′ = H
R = 3,4,5-$(MeO)_3$; R′ = 4-F
R = 3,4,5-$(MeO)_3$; R′ = 4-Cl
R = 3,4,5-$(MeO)_3$; R′ = 4-MeO
R = 3,4,5-$(MeO)_3$; R′ = 3,4-$(MeO)_2$
R = 3,4-$(MeO)_2$; R′ = 4-Cl
R = 3,4-$(MeO)_2$; R′ = 4-MeO
R = 4-F; R′ = 3,4,5-$(MeO)_3$
R = 4-Cl; R′ = 3,4,5-$(MeO)_3$
R = 4-MeO; R′ = 3,4,5-$(MeO)_3$
R = 3,4-$(MeO)_2$; R′ = 3,4,5-$(MeO)_3$
R = 3-Cl, 4-MeO; R′ = 3,4,5- $(MeO)_3$
R = 3,4-Cl_2; R′ = 3,4,5-$(MeO)_3$
R = 4-Cl; R′ = 3,4-$(MeO)_2$
R = 4-MeO; R′ = 3,4-$(MeO)_2$
R = 3-Cl, 4-MeO; R′ = 3,4-$(MeO)_2$
R = 3-Cl, 4-MeO; R′ = 4-Cl
R = 4-Cl; R′ = 3,4-Cl_2

scheme 1. Synthesis of1,4-Diaryl imidazole-2-thione

reagents and conditions: a: $NaHCO_3$, MeOH,25°C ; b: NH_4SCN,10% aqHCl, reflex,1.5h

2.2. Synthesis of 4,5-diphenyl-1,3-dihydroimidazole-2-thione 1

Starting from readily accessible reactants, benzoin asa two carbon component and thiourea as a three atom component. The reaction was first attempted conventionally Benzoin and thiourea were refluxed in hexanol for 4hrs, in the presence of HCl which gave respective imidazole-2-thiones in 50% yield. With a view to devise asimpler, better and greener rout the synthesis was then performed over different solid supports, acidic alumina /montmorillonite under microwaves. The reactantsin appropriate mole ratio were adsorbed over acidic alumina /montmorillonite K-10 clay and were irradiatedunder microwave to afford 4,5-diaryl imidazole-2-thione in 72% .The inorganic solid support used acted as energy transfer medium and catalyst as well eliminating the addition of HCl to facilitate the reaction. Decreased reaction times and increased reactivity of the reactants insolid state with large surface area especially when coupled with microwave as compared to conventional procedure[41]scheme 2.

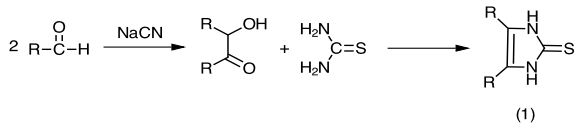


scheme 2.Synthesis of4,5-diphenyl-1,3-dihydroimida

zole-2-thione

2.3. Synthesis of 4,5-diaryl-imidazole-2-thiones 1.

Reaction of aryl aldehyde in the presence of NaCN in a simple one-pot reaction gave a cyloins which were subjected to condensation with thiourea to give 1[42]scheme 3.

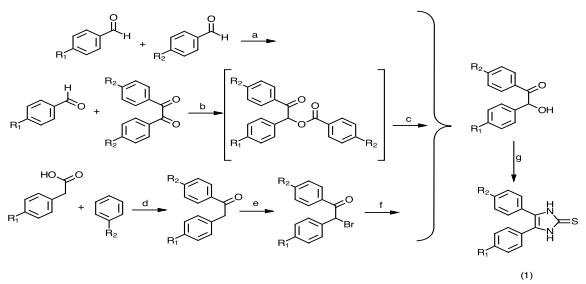


R= p-$CH_3C_6H_4$, R= Ph-Benzoin

R= p-$CH_3OC_6H_4$, R= Ph –p-OCH_3 Anisoin

scheme 3 . Synthesis of4,5-diaryl-imidazole-2-thione

Treatment of different benzoins with a ten-fold excess of ammonium thiocyanate in n-butanol afforded the desired 1 in good yield .A series of 4,5-diaryl-1H- imidazole -2(3H) thione 1 was synthesized and their inhibtory potency againt soybean 15-lipoxygenase and free radical scavenging activities were determined. Structure – activity relationship studies showed that the nature of substituent of two arly (R_1 and R_2) on the imidazole ring had a profound influence on LOX activity[43]scheme 4.



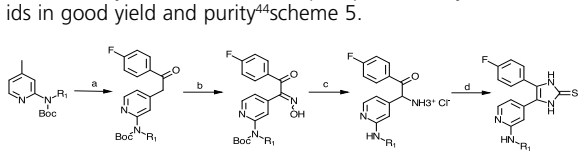
R= H , CH_3 R_1= H,Cl ,F,CH_3S, CH_3O , $(CH_3)_2N$, R_2= H , CH_3O , F , Cl

scheme 4.Synthesis of4,5-diaryl-1H- imidazole -2(3H) thione

reagents and conditions: a: KCN, CH3OH/H2O, reflux; b: KCN, DMF, rt; c:NaOH, CH_3CN, rt; d: H_3PO_4, $(CF_3CO)_2O$, 25 C; e: Br_2, glacial AcOH, rt; f: CH_3ONa, CH_3OH, reflux, 10% HCl; g: NH_4SCN, n-butanol, reflux.

2.4. Synthesisof novel 4(5)-aryl -5(4) -heteroaryl-imidazole-2-thione 1

The straightforward synthesis of imidazole-2-thiones 1a-h from picolines is presented in scheme 5 .Picolines were deprotonated with sodium hexamethyldisilazane (NaHMDS) in THF at 0 °C and reacted with ethyl 4-fluorobenzoate to afford ethanones. The reaction was quenched with aqueous NH_4Cl-solution and purified by flash chromatography, thus allowing the recovery of unreacted starting material picolines. Upon treatment with sodium nitrite (3.0 equiv.) in acetic acid at 10 °C ethanoneswere converted into the α-hydroxyiminoketones. The oximes were obtained as colourless foams and as a mixtureof isomers, indicated by proton NMR. In methanolic hydrogen chloride, the oxime functionality was reduced in the presence of Pd/C under a hydrogen atmosphere at room temperature and atmospheric pressure to an amino group. This step was accompanied by cleavage of the Boc-group as well as by transfer of the amines into the corresponding amine hydrochlorides. The hydrochlorides could be used in the next step without further purification. Cyclisation to imidazole thiones was achieved by heating hydrochlorides and potassium thiocyanate in DMF to reflux temperature. After cooling to room temperature and treatment with water, the imidazole-1,3-dihydro-2-thiones 1a-h precipitated as yellowish solids in good yield and purity[44]scheme 5.



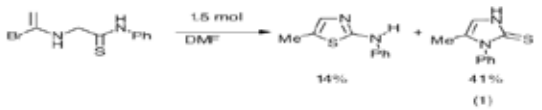
R_1= 1-phenylethyl , ethyl , 3-methylbut-2-yl , isopropyl , benzyl , isobutyl , sec-butyl , tetrahydropyran-4-yl

scheme 5. Synthesis of 5-(2-(alkyl/phenylamino)pyridin-4-yl)-4-(4-fluorophenyl)-1,3-dihydroimida zol-2-thiones 1

reagents and conditions: a: NaHMDS, ethyl 4-fluorobenzoate, THF, 0°C–rt; b: $NaNO_2$, acetic acid, 10°C rt, 2.5 h; c: Pd/C 10%, MeOH–HCl, H_2, rt, 16 h; d: KSCN, DMF, reflux, 3 h; a yield over 3 steps.

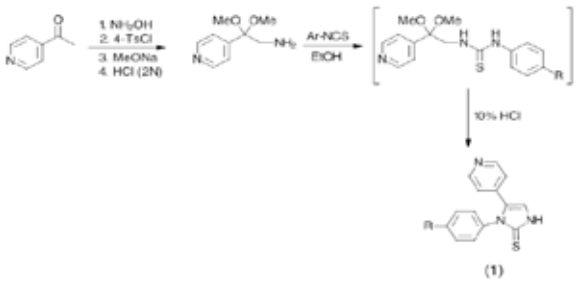
2.5. Synthesis of 1,5-disubstituted imidazole-2-thione1

When N-2-bromoalk-2-enyl-N'-phenylthiourea was treated with k_2CO_3, 2-aminothiazoleand 1,5-disubstituted imidazole-2-thione1 were isolated in 14% and 41% yields , respectively[45]scheme 6.This result demonstrated the competition reaction between S- and N-nucleophiles.



scheme 6 . Synthesis of 1,5-disubstituted imidazole-2-thione

The 1,5-disubstituted imidazole-2-thione3 were afforded by refluxing a mixture corresponding aryl isothiocyanate and aminoacetal in ethanol to form an acetal-thiourea derivative as intermediate which was isolated and immediately heated in equeous 10% HCL via modified method of Marckwald-[46]scheme 7.

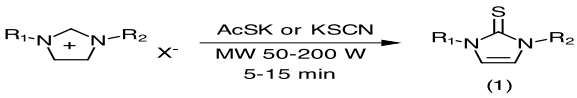


R = 4-NO_2 , 4-Cl , 4-Me , H

scheme 7 . Synthesis of 1,5-disubstituted imidazole-2-thione

2.6. Synthesis of 1,3-disubstituted imidazole-2-thiones 1 under microwave irrdidiation and solvent free conditions.

When a mixture of 1,3-disubstituted imidazolium salt and potassium thioacetate was heated under microwave irradiation (50-200W) for 5-15 min., 1,3-disubstituted imidazole-2-thiones 1, could be obtained in moderate yields. When replaced potassium thioacetate with potassium thiocyanate the same products were obtained in improved yield under similar conditions. It is not worthy that the reaction did not work when conventional heating was used.The Bulky group substituted imidazolium salts should give comparatively higher yields than the small group substituted imidazolium salts[47]scheme 8.

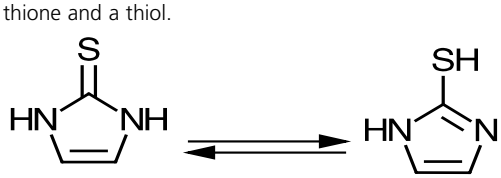


R_1 ,R_2 = Me , Et , $PhCH_2$ X=Cl , Br , I , BF_3

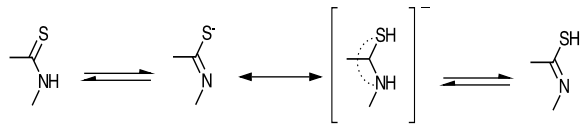
scheme 8 . Synthesis of 1,3-disubstituted imidazole-2-thione

3- Chemical Properties

Imidazole-2-thiones can exist in two tautomeric forms, a thione and a thiol.



Imidazole-2-thiones belong to so-called "ambifunctional nucleophilic compound" and are readily involved in reactions with electrophilic agents. The ambident anion of compounds with a thioamide group, generated by proton abstraction, represents a triatomic moiety II , the negative charge being unevenly distributed between the two end points .



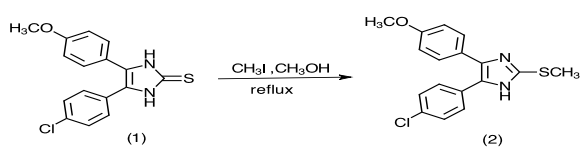
I II III

The interaction of imidazole-2-thione with electrophilic reagents normally involves the readily polarized and highly nucleophilic sulfur atom, In the case of polar electrophiles, however, the new bond is formed with the more electronegative nitrogen atom.Huckel Molecular Orbital (HMO) calculations indicate that thione form is more stable than thiol. A satisfactory correlation between the observed pKa values and the difference between the σ-electronic energies (ΔE) of the thioamide tautomer and of the common resonance stabilized anion has been observed, thus supporting the assigned tautomeric structure. Several reactions have been reported such as preparation of Mannich bases where the N-substitution is done instead of S-substitution which further supports the existence of thione form[48].

3.Reaction of 4,5-diphenylimidazole-2-thione

3.1. Haloalkanes

The alkylation of4,5-diphenylimidazole-2-thione 1 with methyl iodide in methanolthe corresponding S-alkylated in high yield-2[49]scheme 9.



scheme 9

3.2. Carbonyl compounds

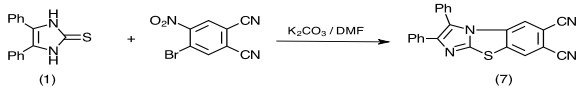
Reaction of 4,5-diphenylimidazole-2-thione 1 with alicyclic ketones like cyclopentanone, cyclohexanone, cycloheptanone, and cyclooctanone in boiling acetic acid, containing a few drops of concentrated sulfuric acid for two hours, afforded the 2-(4,5-diphenyl-2-imidazolylthio) cycloalkanone3 and the cyclized product 2,3-cycloalkano-5,6-diphenylimidazo [2,1-b] thiazole5(a:n =2, b:n=3).Compound 3(a:n=1, b:n=4) were cyclized to the corresponding 4 either by addition of Ac_2O to the reaction mixture or using poly phosphoric acid as the cyclizing agent. Compounds 3-5 showed biological activity against bacterial and fungi[50].The cyclo condensation4,6-dichloro-2-methylthio pyrimidine-5-carbaldehyde with 4,5-diphenylimidazole-2-thione 1 in dimethylformamide at 50-70°C gave tricyclic heterocycles containing a pyrimido [5,4-c] [1,3] thiazine fragment 6[51]scheme 10.



scheme 10

3.3. Nitrilecompounds

Heterocyclic o-dinitrile7 was prepared in high yield and selectivity by the cyclocondensation reaction of 4- bromo -5-nitrophthalonitrile in DMF and in presence of potassium carbonat with thione1[52] scheme 11.



scheme11

A mixture of thione1 , cyclohexylisocyanide and DEAD in toluene , was stirred at room temperature for 6 h to give the imidazo[2,1-b][1,3,4]thiadiazole 8 [53]scheme 12 .

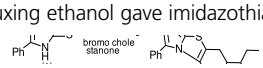


scheme 12

3.4. Chloroacetic acid and Bromocholestanone

The reaction of 4,5-diphenylimidazol-2-thione 1 with chloroacetic acid in presence acetic acid and sodium acetate afforded 5,6-diphenylimidazo [2,1-b] thiazole-3-one 9.Compound 9, when treated with acetic anhydride in presence of sodium acetate, dimethyl formamide-dimethylacetal (DMFDMA), thiophene-2-carbaldehyde and 2-thenylidene activated nitrile gave 5,6- diphenylimidazo [2,1-b] thiazole derivatives 10,12,14 and 7,8-diphenylimidazo [2,1-b] thiazolo [2,3-b] pyran derivatives15,16 .Claisen condensation of compound 10 with diethyloxalate gives 7,8- diphenylimidazo [2,1-b] thiazolo [2,3-b]-4-pyron derivatives 11a,b while 6,7-diphenyl-imidazo [2,1-b] thiazolo [2,3-c] oxazole or (N-phenyl pyrazole)13c,d where obtained directly upon reaction of 12 with hydroxylamine hydrochloride or phenyl hydrazine. Compound from for 9-16 were test for antibacterial and antifungal activity[54] scheme 13.

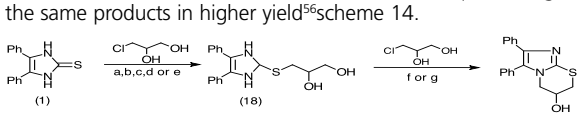
Condensation reaction of bromocholestanone with thion1 in refluxing ethanol gave imidazothiazole derivative 17[55]scheme 13.



SCHEME 13

3.5. 2,3-Dihydroxy Chloropropanol

The regioselective alkylation of 4,5-diphenyl-imidazole-2-thione 1 by reaction with one and two equivalents of 2,3-dihydroxy chloropropanol in boiling solution of sodium ethoxide in ethanol for 2 hours or in boiling methanol in presence of NaOAc for 4 hours afforded only the s-alkyl derivative 18. Further alkylation of the S-alkylated analogues in boiling DMF and in the presence of potassium carbonate afforded imidazo [2,l-b] thiazine 19. This could presumably be due to the ability of K_2CO_3 to abstract the proton from NH group which is not the case with NaOEt or NaOAc. When the above reaction were carried out under microwave (MW), 1-5 minutes were required to give the same products in higher yield[56]scheme 14.



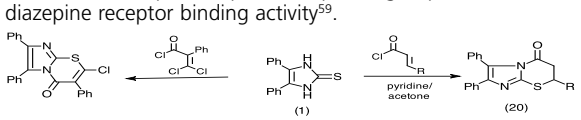
a: NaOEt ,EtOH ,boil , b: NaOEt ,EtOH , MW , c: NaOAc ,MeOH , boil , d: NaOAc ,MeOH , MW , f: K_2CO_3 , DMF , boil , g: K_2CO_3 , DMF , MW

scheme 14

3.6. Activated double bonds

The reaction of 4,5-diphenylimidazole-2-thione1 with acryloyl chloride (R=H), crotonyl chloride (R=Me) and 3-ary1-2- propenoyl chlorides (R=ph) in pyridine and acetone afforded 7- substituted 6,7- dihydro-5H-imidazo [2,1-b] [1,3] thiazine-5-ones 20 [57].

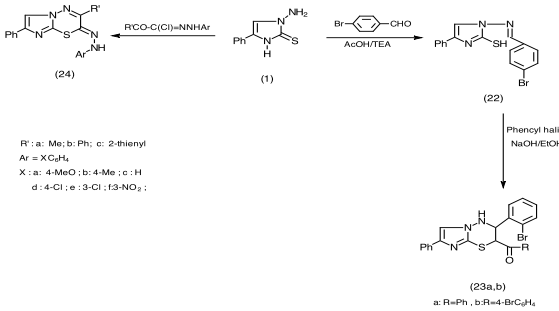
3,3-Dichloro-2- phenyl acryloylchloride was directly transformed into imidazo [2,1-b] [1,3] thianzin-5-one 21 by condensation with thione1[58]scheme 15.Imidazo [2,1-b] [1,3] thiazine is an important pharmacophoric group for the benzodiazepine receptor binding activity[59].



scheme 15

3.7. Synthesis of 3,4-dihydro-2H- imidazo-[2,1-b] [1,3,4] thiadiazine derivatives

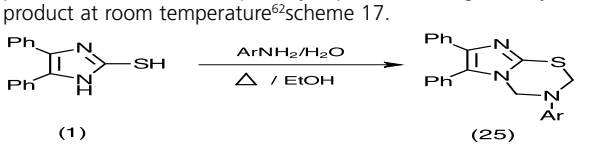
A- The condensation of 1-amino-4- phenylimidazole-2-thione 1 with p-bromobezaldehyde gave the corresponding aldimine 22. The alkylation of 22 by phencyl halides gave imidazothiadiazine 23[60]. Reaction of N-aryl-2-oxohy-drazonoyl chlorides with compound 1 in ethanol in the presence of sodium ethoxide at room temperature afforded 2-arylazo-4H-imidazo [2,1-b] [1,3,4] thiadiazine 24 .This finding indicates that the initially formed thiohydrazonates undergo in situ dehydrative cyclization as soon as they are formed to give 24 as end products[61]scheme 16.



scheme 16

B- Mannich Reaction

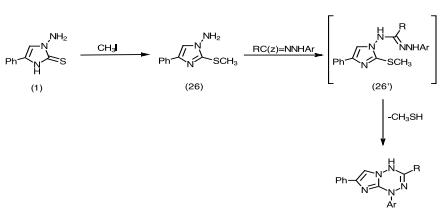
Condensation of imidazole-2-thione 1 with formaldehyde and primary aromatic amine in boiling ethanol gave bicyclic products 25 ; while with primary aliphatic amine gave bicyclic product at room temperature[62]scheme 17.



scheme17

3.8. Synthesis of imidazo [1,2-b] [1,2,4,5] tetrazines

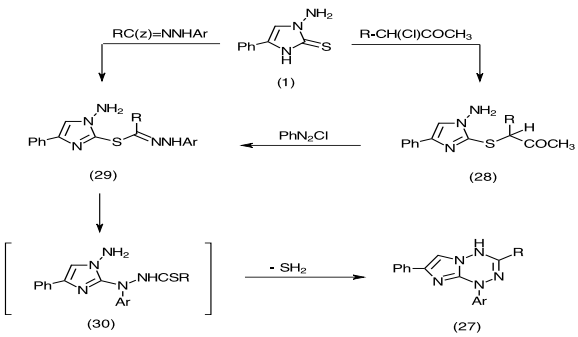
Methylation of 1-amino-2-thio-4-phenylimidazole 1 gave 1-amino-2-methylthio-4-phenylimidazole 26. Refluxing equimolar quantities of each of the hydrazonoyl halides with compound 26 in ethanol in the presence of triethylamine or sodium ethoxide gave in each case one product 27. To account for the formation of the latter products 27. It is suggest, as depicted in scheme 18,



R= a:Ph/H; b:Ph/NO_2; c:PhCH=CH/ H; d:EtOCO/H; e:EtOCO/NO_2; f:EtOCO/Me; g:EtOCO/Cl; h:PhNHCO/H; i:PhNHCO/NO_2; j:PhNHCO/Me; k:PhNHCO/Cl; l,2-thienyl/NO_2; m: CH_3CO/H; n, CH_3CO/NO_2; o: CH_3CO/Me; p: CH_3CO/Cl; q: PhCO/H; r:PhCO/Me; s:PhCO/Cl; t: 2-naphthoyl/Me; u:PhCO/NO_2; v: 2-thenoyl/H

scheme 18

That the reaction of 26 with hydrazonylhalids involves the initial formation of the hydrazidines intermediate 26` which subsequently undergo in situ cyclization with elimination of methanethiol to give 27 as end product. The assignment of the structure 27 for the isolated products was further evidenced by the alternate synthesis of compound 27a,27c, 27d, 27h and 27i as typical examples of the series prepared scheme 19. The compounds 27a-i were tested for their antimicrobial activities against fungi and bacteria, the compounds 27b,27e, 27i, 27j and 27i exhibited the highest degree of inhibition against the test bacteria species. The activates of all such compounds are similar to the standard antibacterial agent used[63].

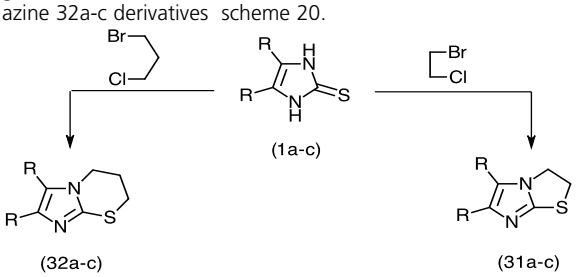


Z = Cl, Br; Ar = 4-XC_6H_4 R= a:Ph/H; c:PhCH=CH/H; d:EtO-CO/H; h: PhNHCO/H; l, 2-thienyl/NO_2

scheme 19

3.9. Synthesis of 3,4-disubstituted-6,7-dilydroimidazo [2,1-b] [1,3] thiazole and 3,4-disubstituted 7,8-dihydro-6H- imidazo [2,1-b] [1,3] thiazine derivatives.

A. Cyclization of 4,5-diaryl-imidazole-2-thione 1a-c and dihaloalkane (i.e., 1,2-dihaloethane or 1,3-dihalopropane) in the presence of potassium carbonate in N,N-dimethyl formamide gave imidazo[2,1-b] thiazole 31a-c and imidazo [2,1-b] thiazine 32a-c derivatives scheme 20.



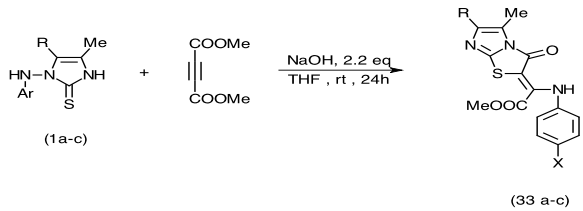
a: R=C_6H_5 , b: R= p-$CH_3C_6H_4$, c: R= p-$OCH_3C_6H_4$

scheme20

The cytotoxicites of the synthesized compounds on both of non cancer (F2408) and cancer (5RP7) cell were measured. Some compounds showed does and time dependent cytotoxic effects on both cell lines . In the presence of only lower doses of compounds 31b and 31c bearing methyl or methoxy substituents on the phenyl ring of imidzao [2,l-b] [1,3] thiazole, the cytotoxic effect was higher on (5 RP7) cells than control cells after 24h[64].

Reaction of 1- arylamino- imidazole-2-thione la-c with dimethyl acetylene dicarboxylate (DMAD) in the presence of (2.2 equiv.) of sodium hydride, imidazothiazoles 33a-c were exclusively formed (71-82% yield), through a novel arylamino rearrangement[65]

1-Arylamino-imidazole-2-thionela-c[66] were selected, since the enhanced reactivity of the sulfur over the 3NH and 6NH positions is well documented[67]scheme 21.



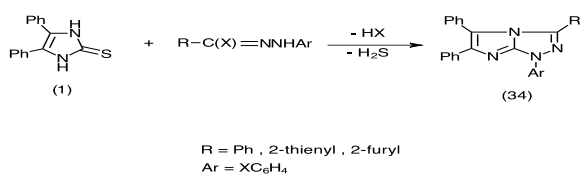
a: R=Me , Ar=C_6H_5 , b: R=Me , Ar= p-ClC_6H_4 , c: R= C_6H_5 , Ar= C_6H_5

scheme21

Among the fused azole heterocycles with bridgehead nitrogen, imidazo[2,l-b] [1,3] thiazole have received considerable attention as a result of their various biological effects. These activities rang from antibacterial[68], antimicrobial[69],antituberculosis[70],antisecretory[71]and antitumor[72].

3.10. Synthesis of imidazo [2,1-c] [1,2,4] trizole derivatives

Treatment of 4,5 -diphenylimidazoline- 2(3H)-thione1 with hydrazonoyl halides having no α oxo-group in chloroform in the presence of triethylamine gave compound 34 directly[73]scheme 22.



scheme22

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