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Pharmaceutical Importance and Synthetic Strategies for Imidazolidine-2-thione and Imidazole-2-thione Derivatives

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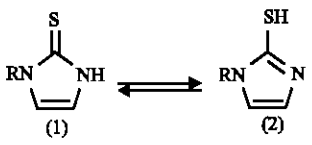
Abstract: Imidazole heterocycles containing oxygen or sulfur heteroatoms are of considerable pharmaceutical interest. Many synthetic strategies for imidazolidine-2-thione and imidazole-2-thione derivatives were developed in the past years. They have been well documented by a steadily increasing number of publications and patents. Substituted imidazolidine-2-thiones and imidazole-2-thiones display remarkable biological activities. For instance, imidazole-2-thione has been reported to exhibit antimicrobial, antifungal, antithyroid, antioxidant, cardiotonic, antihypertensive, Dopamine β-Hydroxylase (DBH) inhibitory and anti-HIV properties. Imidazolidine-2-thione derivatives have been reported to exhibit antimicrobial activity, anti-HIV activity, antifungal activity and so forth. The main purpose of this review is to present a survey of the literature on the different methods of synthesis and reactions involving imidazolidine-2-thione and imidazole-2-thione during the last few decades. This article summarizes an efficient, microwave-assisted method for the liquid-phase combinatorial synthesis of 3,5-disubstituted-thiohydantoin, also reported previously. Synthesis of metal complexes of imidazolidine-2-thione and its derivatives were reported as antimicrobial agents also discussed in the article. Some of the chiral imidazolidine-2-thione N-and C-nucleoside were reported as precursors for the synthesis of azidonucleosides and fluoronucleosides known for their anti-AIDS activity. Metal complexes of heterocyclic thione ligands were reported to possess antifungal activity. Imidazolidine-2-thione and imidazole-2-thione derivatives have found applications in diverse therapeutic areas. Imidazolidine-2-thiones are also used as a chiral auxiliary and ligand for asymmetric catalysis.

Key words: Anti HIV activity, antihypertensive activity, imidazole-2-thione, imidazolidine-2-thione, imidazolidinone, microwave synthesis, solid phase synthesis, thiohydantoin

INTRODUCTION

During the past decades chemistry, synthesis and transformations of five member heterocyclic compounds have received considerable attention and importance due to their remarkable and wide variety of applications (Briganti *et al*., 1996). They have been well documented by a steadily increasing number of publications and patents.



R = H, alkyl or aryl group

Imidazole-2-thiones are an interesting class of compounds. The synthesis and evaluation of oxygen and nitrogen analogs of the soft thione group demonstrated that the S atom is necessary for optimal activity (Kruse *et al*., 1990).

Imidazole-2-thione is known to exhibit tautomerism as thione (1) and thiol (2). It is also indicated that the ionization of the compounds occur from the thione form. 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 (Ferraroni *et al*., 2002).

A detailed account of the various methods of synthesis, reported biological activities and synthetic usefulness is described in the following sections.

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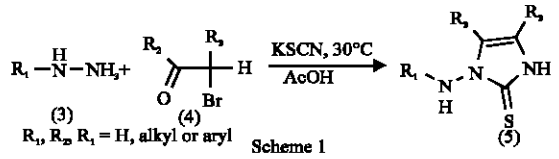
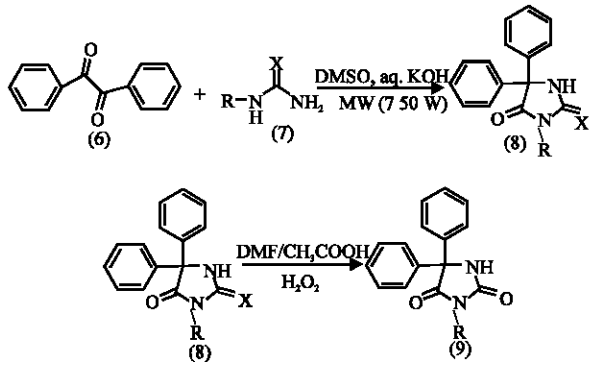
SYNTHETIC PROCESSES OF IMIDAZOLIDINE-2-THIONES AND IMIDAZOLE-2-THIONES

Synthesis of N-aminoimidazoline-2-thione was reported by Lagoja *et al*., 2003. N-substituted 1-amino-2,3-dihydro-1H-imidazole-2-thiones(5) were formed in good yield in a one pot reaction of hydrazine (3), bromoketones (4) and potassium thiocyanate (Scheme 1). The same report also discusses the antiretroviral activity as well as cytotoxic activity of the compounds studied. Structure Activity Relationship (SAR) of imidazole-2-thione derivatives shows that methylation or benzylation of sulfur led to complete abolishment of antiviral activity. Smaller substitutents like methyl or ethyl at position 4 of imidazole ring leads to more pronounced antiviral activity. The nature of substitutions on the anilino substituent at position 1 of the imidazole ring has serious repercussions on the antiviral activity of the N-aminoimidazoline-2-thiones reported by the research group. It was reported that these substitutions influence the potency; more importantly they influence the activity spectrum of the molecules. The most active molecules were reported to be the meta-substituted anilino derivatives. The active molecules bearing chlorine at position 3 of the anilino phenyl ring had a broader activity spectrum. Although the exact molecular target remains to be resolved, the reported experiments clearly indicate that some of the N-aminoimidazoline-2-thione derivatives interfere with an immediate postintegrational event occurring after integration of the viral DNA into the host cell genome (Lagoja *et al*., 2003).



Scheme 1

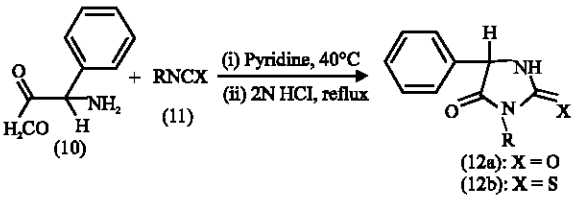
Muccioli *et al*. (2006) synthesized 5,5-diphenyl-2-thioxoimidazolidin-4-one(8)and5,5-Diphenylimidazolidine -2,4-dione (9) derivatives from the respective benzil (6) and urea (7, X = O) or thiourea (7, X = S) derivatives using a microwave-enhanced method. The method allowed rapid synthesis of the target derivatives (8) in moderate to good yields. It has been reported that, when phenylurea was used, the resulting compound obtained was 1-benzhydryl-3-phenylurea instead of the target 3-substituted imidazolidine-2,4-dione.3,5,5`-triphenylimidazolidine-2,4-dione (9) was obtained in high yield from the corresponding 2-thioxoimidazolidin-4-one (8) upon reaction with hydrogen peroxide in dimethylformamide-acetic acid medium (Scheme 2). Imidazolidine-2,4-dione and 2-thioxoimidazolidin-4-one derivatives was also evaluated by the research group as fatty acid amide hydrolase (FAAH) inhibitors which is essential for hydrolyzing endogenous bioactive fatty acid derivatives (Muccioli *et al*., 2006).



Where in, X is O or S R is hydrogen, alkyl, alkularyl

Scheme 2

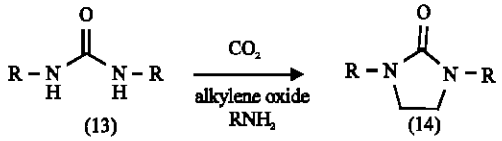
3-substituted 5-phenylimidazolidine-2,4-dione (12a) and 3-substituted 5-phenyl-2-thioxoimidazolidin-4-one (12b) derivatives were synthesized in two steps by reacting phenylglycine methyl ester (10) with the desired phenyl or alkyl isocyanate/isothiocyanate (11, X = O or S), respectively. The first step consisted of the condensation of the amino acid derivative with a phenyl or alkyl iso(thio)cyanate in pyridine, leading to 3-substituted (thio)ureido-phenyl acetic acid. The second step allowed the cyclization of the acid derivative upon refluxing in aqueous acidic medium (Scheme 3) (Muccioli *et al*., 2006).



Where in, X is O or S, R is hydrogen, alkyl, alkylaryl, alkylether, hydroxy alkyl

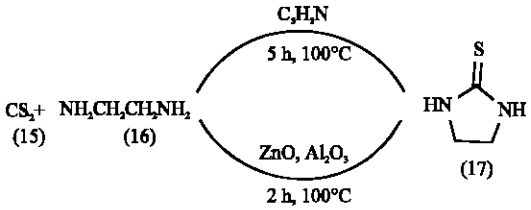
Scheme 3

US patent 6,861,534 describes an industrial process for preparing 1,3-dialkyl-2-imidazolidinone (14) using an alkylene oxide as a first component, carbon dioxide and a monoalkylamine or a carbon dioxide compound of the monoalkylamine; and an 1,3-dialkylurea(13). Heating first and second components at 50° C or higher gave 1,3-dialkyl-2-imidazolidinone(14). The characteristic feature of this invention is the utilization of industrially available alkylene oxide as a starting material which can be suitably conducted with a higher yield on an industrial scale (Scheme 4) (Katsuhiko *et al*., 2005).



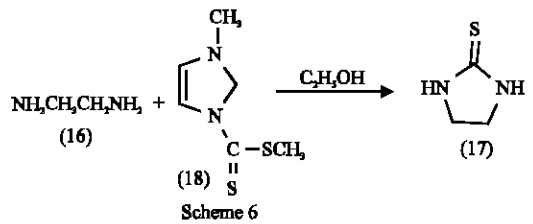
Scheme 4

Imidazolidine 2- thione (17) was synthesized by Zhivotova and co-workers using a mixture of ethylene diamine (16) and carbon disulfide (15) in pyridine under reflux for 5 h on water bath. The resulting reaction mixture was poured in to ice cold water and acidified with glacial acetic acid affording imidazolidine-2-thione (17) as depicted in Scheme 5 (Zhivotova *et al*., 2006). Synthesis of symmetrical *N,N`*-disubstituted thioureas and heterocyclic thiones from amines and CS_2 over a ZnO/Al_2O_3 composite as heterogeneous and reusable catalyst was reported by Ballabeni *et al*. (1999). The synthesis of imidazolidine-2-thione was carried out by the reaction of ethylene diamine(16), carbon disulfide(15) and the heterogeneous catalyst in a small autoclave equipped with a stirrer, at 100°C for 2 h (Scheme 5) (Ballabeni *et al*., 1999).



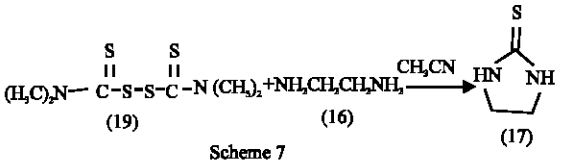
Scheme 5

1-(Methyldithiocarbonyl)imidazole(18) and its N-methyl quaternary salt have been shown to be efficient methyldithiocarbonyl and thiocarbonyl transfer reagents. They act as transfer reagent for the synthesis of dithiocarbamates, symmetrical and unsymmetrical mono-, di- and tri-substituted thioureas in high yields. Mixture of 1-(methyldithiocarbonyl)imidazole(18) and ethylenediamine(16) in ethanol was reacted by Mohanta *et al*. (2000) for 2.5 to 5 h affording imidazolidine -2-thione (17) (Scheme 6) (Mohanta *et al*., 2000).



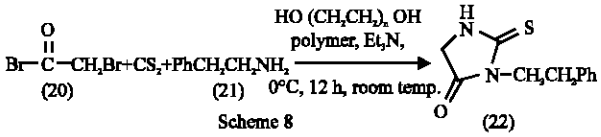
Scheme 6

A variety of substituted cyclic thioureas (imidazolidine-2-thione (17)) were resulting from the reaction between thiourea disulfides (19) and different amines ethylene diamine (16) and methyl cyanide (Scheme 7) (Ramadas and Srinivasan, 1995).



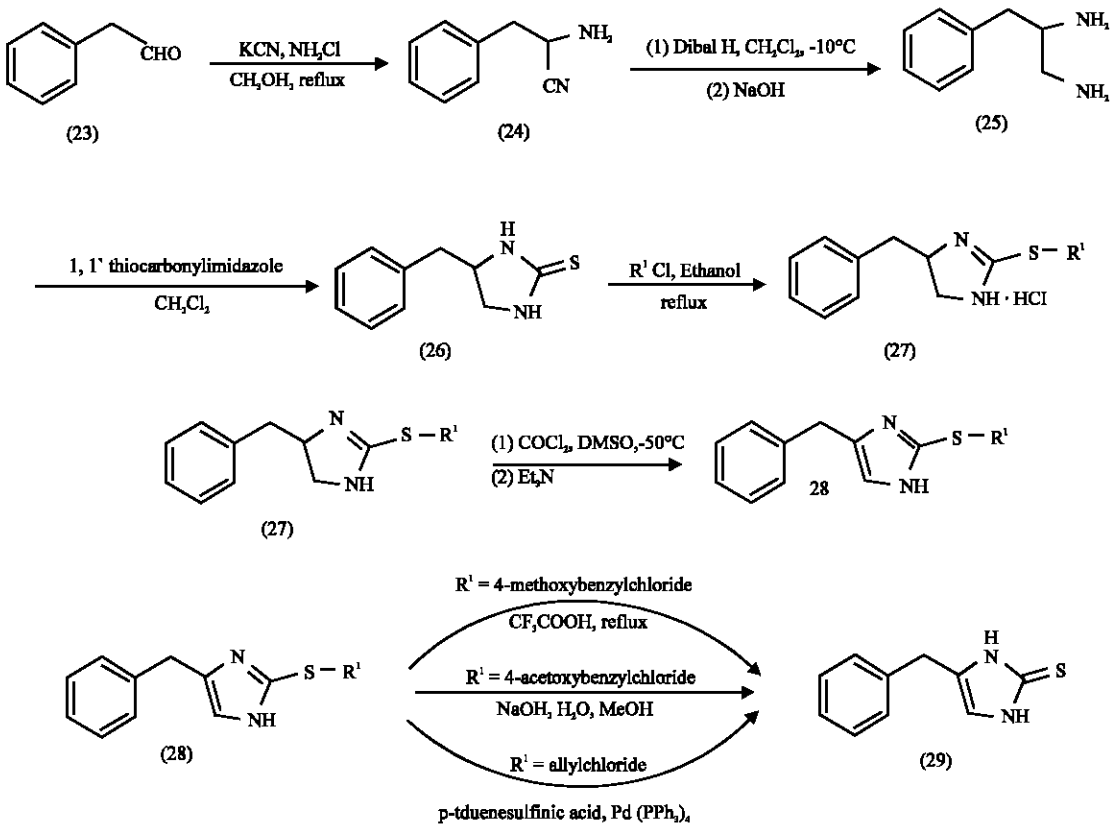
Scheme 7

A novel method for the liquid-phase combinatorial synthesis of 3-substituted-2-thiohydantoin has been developed using poly (ethylene glycol)-supported isothiocyanate. The PEG-supported isothiocyanate was obtained from the reaction of PEG with bromoacetyl bromide (20), followed by an Aza-Wittig reaction. Reaction of PEG-supported isothiocyanate with various aliphatic amines and carbon disulfide (phenyl ethylamine (21)) offered 3-substituted 2-thiohydantoins (22) in excellent yields with addition, cyclization and cleavage reactions occurring in one pot (Scheme 8) (Xiang *et al*., 2008).



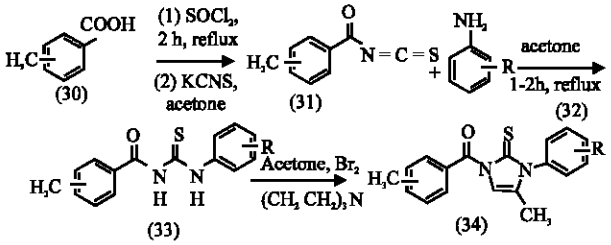
Scheme 8

US patent 7,115,748 describes a method of making an imidazole-2-thione which comprises the steps of reacting a vicinal diamine with a compound having a thiocarbonyl moiety and oxidizing the resulting reaction product to obtain the said imidazole-2-thione (29). The first step of the sequence, the Strecker synthesis with phenylacetaldehyde (23), yields amino nitrile (24). Reaction of various suitable aldehydes, also yields imidazole-2-thione with different R substituents. Dibal reduction of 2-amino-3-phenylpropanenitrile (24), gave 3-phenyl-1,2-diaminopropane (25) in 68% yield after distillation. Dibal (Diisobutylaluminium hydride) was the best of several reducing agents tried by Michael *et al*. (2006) for the reduction of 2-amino-3-phenylpropanenitrile (24). Treatment of 3-phenyl-1,2-diaminopropane with 1,1`-thiocarbonyldiimidazole rapidly produced 4-benzyl-2-imidazolidinethione (26). Before oxidation sulfur group was protected by reaction with aryl halide. Alkylation with benzyl chloride, p-methoxybenzyl chloride, p-acetoxybenzyl chloride or allyl chloride resulted in alkylated sulfur. Swern oxidation of the resulting isothiouronium salts (27) gave the protected imidazole derivatives (28). Deprotecting the p-methoxybenzyl derivative with acid, the p-acetoxybenzyl derivative with base and the allyl derivative with p-toluenesulfinic acid in the presence of a catalytic amount of tetrakis (triphenylphosphine) palladium $(Pd(PPh_3)_4]$ afforded 4-benzylimidazolidine-2-thione (29) (Scheme 9) (Michael *et al*., 2006).



Scheme 9

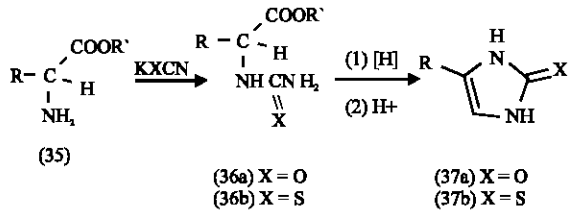
The isomeric methyl benzoic acids (30) were converted into the corresponding acid chlorides using thionyl chloride, then treated with a solution of potassium thiocyanate in acetone to yield aryl isothiocyanate (31) *in situ*, followed by refluxing with substituted anilines (32) to provide 1-isomeric methylbenzoyl thioureas (33) in high yields as reported by Saeed and Batool, 2007. Reaction of 1-(isomeric methyl)benzoyl-3-arylthiourea (33) in dry acetone in presence of bromine provided the 1-tolyl-3-aryl-4-methylimidazole-2-thione (34) (Scheme 10).



R = H, 3-Cl, 4-Br, 3-CH_3, 3-OCH_3, 2-Cl, 4-Cl, 2-CH_3, 2-OCH_3

Scheme 10

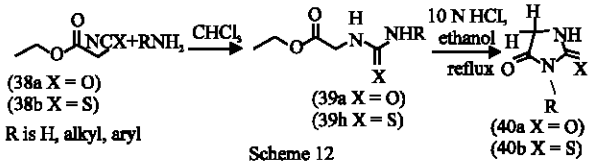
US patent 2007/0197795 describes a method for the synthesis of 4-substituted imidazole-2-one and thiones. Substituted methylene urea (36a) or thiourea (36b) was synthesized by Michael *et al.* (2007) by the reaction of substituted primary amine (35) with potassium cyanate or potassium thiocyanate respectively for one hour at room temperature. The solution of substituted methylene urea (36a) or thiourea (36b) in dichloromethane was then cooled to -40°C and a solution of diisobutylaluminium hydride (Dibal) was added slowly with stirring. The reaction mixture was then acidified with mixture of conc. HCl and crushed ice resulting in the formation of 4-substituted imidazole-2-one(37a) or thione (37b) (Scheme 11) (Michael *et al*., 2007).



R = alkyl, aryl, alkyl aryl radicals, alkyl aryl radicals substituted with halogen, nitrogen, oxygen, sulfur or phosphrous, R` = alkyl having from 1 to 6 carbon atoms, X = O or S

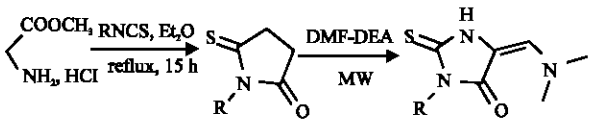
Ryczek (2004) reported the use of ethyl 2-isocyanatoacetate (38a, X = O) and an amine to refluxing

in chloroform afford the 3-substituted ureidoacetic acid ethyl ester (39a) on refluxing in chloroform which on further refluxing in ethanolic hydrochloric acid cyclized to form the imidazolidine-2,4-dione nucleus bearing the desired substituent in position 3 (40a). Following the same procedure but starting from glycine ethyl ester isothiocyanate (38b, X = S) the 3-substituted 2-thioxoimidazolidine-4-one derivatives (40b) were obtained in good yields (Scheme 12) (Ryczek, 2004).



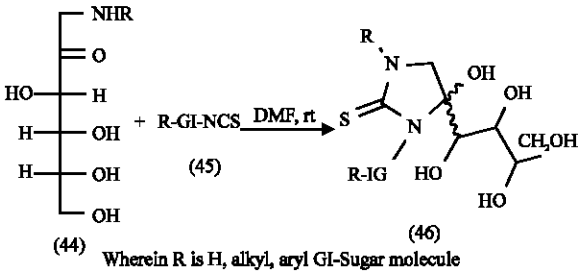
Scheme 12

A practical and ecofriendly synthesis of 3-alkyl-5-dimethyaminomethylidene-2-thioxo-imidazolidin-4-one derivatives from 2-thiohydantoins was reported by Cherouvrier *et al.* (2002) without the use of any solvent. The preparation of 3- alkyl-5-dimethylaminomethylene-2-thioxo-imidazolidin- 4-ones (43) was reported by the reaction between 3-substituted-2-thioxo-imidazolidin-4-ones (42), alkyl and aryl isothiocyanates and methyl glycinate hydrochloride (41) in basic medium. The reactivities of 2-thioxo-imidazolidin-4-ones derivatives (42) with N, N-dimethylformamide diethylacetal (DMF-DEA) using solvent-free conditions under microwave irradiation was investigated by the research group. The 2-thioxo-imidazolidin-4-ones (42) were converted with DMF-DEA (1.05 equiv.) into the corresponding 5-dimethylaminomethylidene-2-thioxo-imidazolidin-4-ones (43) in yields ranging from 74 to 77% after a reaction time of around 30 min at 70-80°C (Scheme 13) (Cherouvrier *et al.*, 2002).



Scheme 13

Gasch *et al.* (2000) reported the synthesis of optically pure 1-aryl-5-hydroxy-4-(D-arabino-tetritol-1-yl)-imidazolidine- 2-thione (46) used as a chiral auxiliary and ligand for asymmetric catalysis. The literature describes the reaction of D-fructosamines (44) with different sugar isothiocyanates (45) to obtain chiral imidazolidine-2-thione N-nucleosides (46) (Scheme 14) (Gasch *et al.*, 2000).



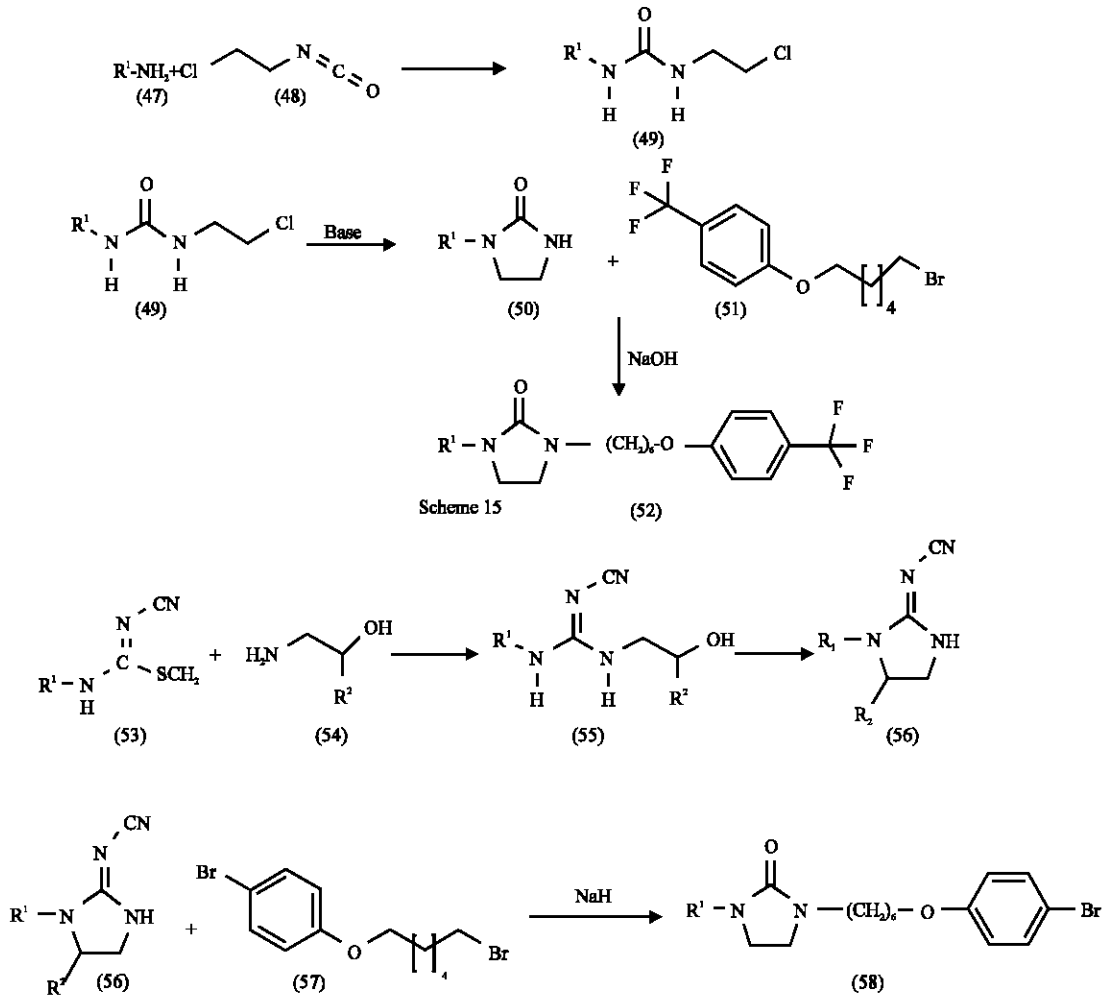
Scheme 14

US patent 2003/0087936 details the method of synthesis of imidazolidinone compounds and also described the method of treating enterovirus infection. The compounds of the invention can be used as antiviral agents, particularly against human enterovirus. The patent discloses the possibility of the compounds being administered via a parenteral route. The active compound dissolved in Phosphate Buffered Saline (PBS), or admixed with any other pharmaceutically acceptable carrier can be administered for treating human enterovirus.

Two methods for the synthesis of imidazolidinones have been described in this patent. In the first method N-(2-chloroethyl) urea (49) was obtained by the reaction between substituted amine (47) and 1-chloro-2-isocyanatoethane (48). N-(2-chloroethyl) urea (49) in the presence of a suitable base gave the imidazolidinone (50) precursor followed by alkylation reaction with 1-bromo-6-[4-(trifluoromethyl)-phenoxy]hexane (51) reaction affording N-alkoxy substituted imidazolidinones (52) (Scheme 15) as described in the patent.

In second method reaction between substituted N`-cyano-N-methylcarbamimidothioate (53) and substituted 2-hydroxyethyl amine (54) by activating its hydroxyl group resulted in the formation of a 4-substituted cyanoguanidine (55) intermediate and finally gave N-(imidazolidin-2-ylidene)cyanamide (56) by intramolecular cyclization. N-(imidazolidin-2-ylidene)cyanamide (56) was then alkylated with (e.g. 1-[(6-bromohexyl)oxy]-4-bromobenzene (57)) yielding substituted imidazolidinones (58) (Scheme 16).

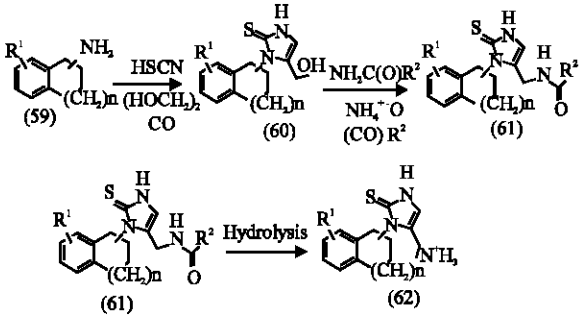
In Schemes 15 and 16, R^1 and R^3, refers to C_{6-12} aryl, C_{6-12} aralkyl, or heteroaryl, optionally substituted with one or more halogen, ether, nitrile, ketone, sulfonyl compounds. R^2 refers to H, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{6-12} aryl, C_{6-12} aralkyl, or heteroaryl, optionally substituted with one or more halogen, ether, nitrile, ketone, sulfonyl compounds (Kak-Shan *et al.*, 2003).



Scheme 15

Scheme 16

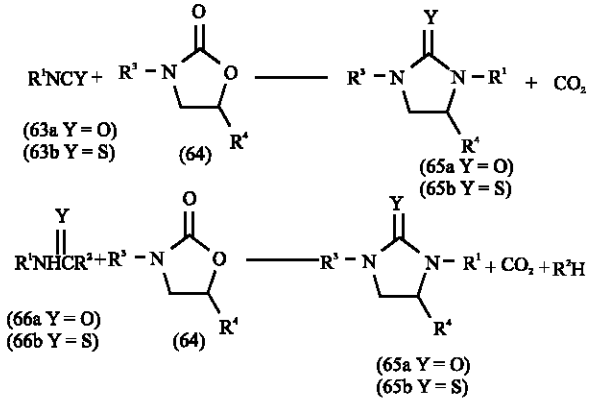
US patent 5,438,150 relates to a process for preparing 5-(N-substituted)aminomethyl-1-benzocycloalkyl-1,3-dihydroimidazole-2-thione (61). Reaction of benzocycloalkylamine (59) with thiocyanic acid and dihydroxyacetone gave 5-hydroxymethyl-1-benzocycloalkyl-1,3-dihydroimidazole-2-thione (60). Further reaction with substituted alkyl amide yielded different substituted imidazole-2-thione derivatives (61). The invention also relates to a process for preparing 5-aminomethyl-1-benzocycloalkyl-1,3-dihydroimidazole-2-thiones (62) which comprises preparing a 5-(N-substituted)aminomethyl-1-benzocycloalkyl-1,3-dihydroimidazole-2-thione (61) by the process described above and then hydrolyzing with acid. Here, R^1 is independently selected as halo, hydroxyl of (C_{1-4}) alkyloxy; and the free base, individual isomers and mixtures of isomers, R^2 is hydrogen, amino, (C_{1-4}) alkyl or trifluoro (C_{1-4}) alkyl and n is 0, 1 or 2 (Scheme 17) (Bansal *et al*., 1995).



Scheme 17

US patent 4,642,351 describes the process for the preparation of N-substituted imidazolidinones (65a Y = O) and N-substituted 2-thionimidazolidinones (65b Y = S) which comprises contacting an oxazolidinone(64) with a compound containing a nitrogen directly bonded to a carbonyl or a thiocarbonyl group in the presence of a Lewis acid catalyst or the hydrate of a Lewis acid catalyst (Scheme 18). The compound containing nitrogen directly bonded to a carbonyl or a thiocarbonyl group is an isocyanate (63a Y = O) or isothiocyanate (63a Y = S) or a

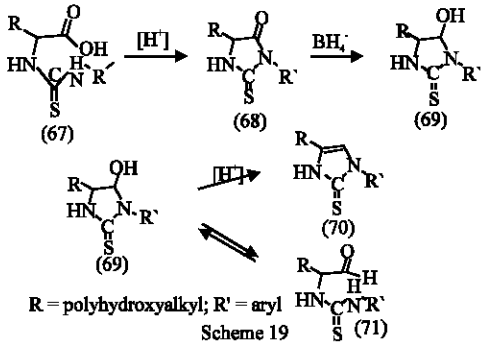
compound wherein the nitrogen is reactive and the carbonyl or thiocarbonyl group is further bonded to a substituent by a bond which is cleavable under the reaction conditions. The Lewis acid catalyst corresponds to the formula "MX_n" wherein M is a group IB-VIIIB, IIIA or IVA element with the proviso that M is not C or Si (Price and Woo, 1987).



R^1 = C1-20 hydrocarbyl radical optionally substituted with halogen, aryloxy, alkoxy, nitro, thioaryloxy, or thiolkoxy group; R^3 = H or a C1-20 hydrocarbyl racical optionally substituted with a halogen, aryloxy, alkyloxy, aryl, or nitro group; R^4 = H or R^3; X-halogen and n = 2, 3 or 4

Scheme 18

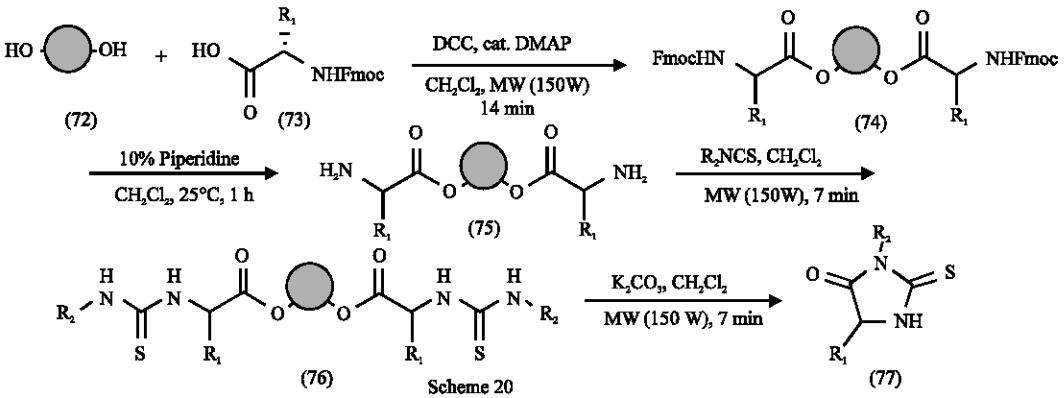
A novel route of synthesis of imidazole-2-thione derivatives has been reported by Scott and Henderson, 1968 using 2-thiohydantoin (68). It is obtained from the reaction of thiohydantoic acid (67) under acidic conditions. Hydroxy imidazolidine-2-thione (69) was prepared by reaction of 2-thiohydantoin(68) with Lithium borohydride and subsequent elimination of water giving imidazole-2-thione derivatives (70). α-Thiocarbamidoaldehyde derivatives (71) were obtained from 5-hydroxy imidazolidine-2-thione derivatives (69) reversibly as depicted in the research article (Scheme 19) (Scott and Henderson, 1968).



R = polyhydroxyalkyl; R' = aryl

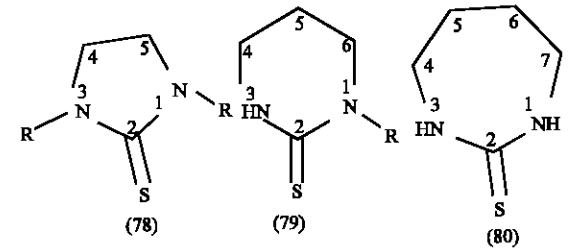
Scheme 19

An efficient, microwave-assisted method for the liquid-phase combinatorial synthesis of 3,5-disubstituted-thiohydantoin (77) has been developed Soluble polymer support (HO-PEG-OH(72)) dissolved in CH_2Cl_2 was coupled with Fluorenylmethyloxycarbonyl chloride (Fmoc) protected amino acids (73) under N,N'-Dicyclohexylcarbodiimide and 4-Dimethylaminopyridine (DCC/DMAP) activation by focused microwave reactor (150 W) for 14 min. For comparison with the conventional thermal heating, coupling reactions were also reported in refluxing methylene chloride (preheated oil bath) for 14 min, using the same stoichiometry. Following deprotection of compound (74) with 10% piperidine in methylene chloride at room temperature, various isothiocyanates in methylene chloride were introduced through 150 W microwave irradiation for 7 min to give thiourea intermediate (76). The control reaction was also reported under normal thermal heating in refluxing methylene chloride (preheated oil bath) for 7 min, under identical stoichiometry. The cyclization/traceless cleavage step was complete under mildly basic conditions (K_2CO_3) with 150 W microwave flash heating for 7 min (Scheme 20). The major advantage of cyclorelease strategy is the fact that only the desired compound is released into the solution. Upon completion of reaction, polymer support was removed from the homogeneous solution to provide the corresponding product in 88-99% yield based on the initial loading to the support (Lin and Sun, 2003).



Scheme 20

The preparation and characterization of new mercuric complexes of formula $L_2Hg(CN)_2$ with L being imidazolidine-2-thione (Imt) and its substituted derivatives (78), 1,3-diazinane-2-thione (Diaz) (79), 1,3-diazipane-2-thione (Diap)(80), is described by Wazeer *et al.* (2007). The complexes were synthesized by reacting $Hg(CN)_2$ with thiones in 1:2 ratio. Antimicrobial activity was reported by evaluating Minimum Inhibitory Concentration (MIC) on four microorganisms, namely Heterotropic Plate Counts (HPC), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Fecal Streptococcus* (FS) and *Escherichia coli* (*E. coli*) (Wazeer and Isab, 2007).

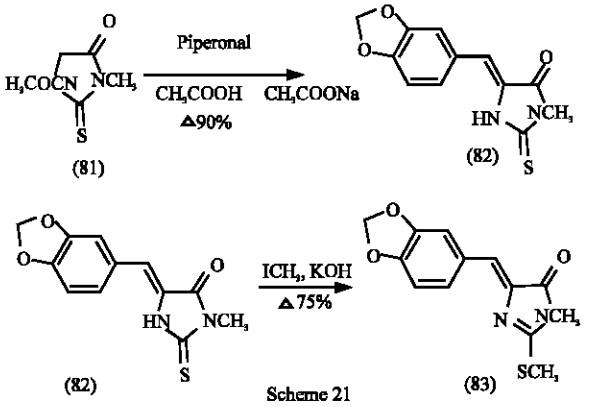


Cadmium chloride complexes with imidazolidine-2-thione and its derivatives(78) were reported by Wazeer *et al.* (2007). The research article reported the solid state and solution NMR as well as X-ray structure studies of $Cd(thione)_2Cl_2$ complexes. Their antimicrobial activities were compared with the corresponding $Zn(thione)_2Cl_2$ complexes. The results of the bioactivity studies showed that the Imt (78) free ligand showed significant antimicrobial activity compared to Diaz (79) and Diap (80). After complexation with Zn(II), the antimicrobial activity was increased. However, the research group also compared Diap and its $CdCl_2$ complex and it was reported that all antimicrobial activities were reduced, indicating the adverse effect of Cd_2^+ ion (Wazeer *et al.*, 2007).

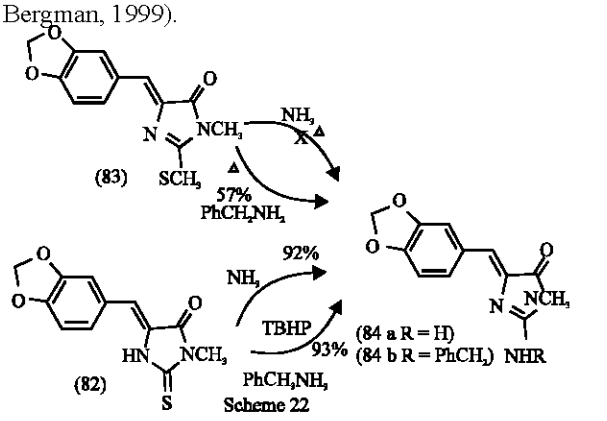
Cyclic sulfates of N- and C-nucleosides (D-*ribo* and D-*erythro* configurations, respectively) were used by Fuentes *et al.* (2002) to prepare 3`-amino C-nucleosides(furan, imidazoline-2-thione and pyrrole derivatives). Reaction of the 3`-amino with the 3`-isothiocyanato C-nucleosides gave thioureylene di-C-nucleosides, a type of nucleotide analogue with a nonionic bridge isostere of the phosphate group which has been reported as an agent in the treatment of AIDS (Fuentes *et al.*, 2002).

Several reactions for the transformation of substituted 2-thiohydantoin into glycocyamidines (83) are known and have been shown to possess an important role as mediators in inflammation. The transformation may be achieved either directly by desulfurizing the 2-thiohydantoins in the presence of amines or indirectly by the ammonolysis of the S-alkyl derivatives of the 2-thiohydantoins (Kruse *et al.*, 1990; Lopez and Trigo, 1985).

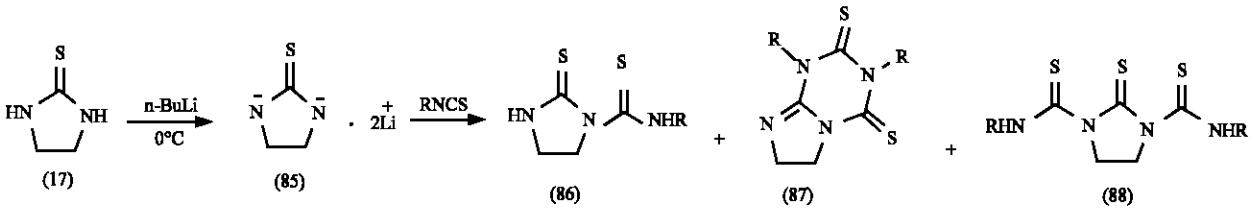
Another efficient method for the synthesis of 2-thiohydantoin derivatives was also reported by the research group. The readily available 1-acetyl-3-methyl-2-thiohydantoin (81) was condensed with piperonal in acetic acid which gave stereochemically pure (Z)-4-(3,4-methylenedioxyphenyl)methylene-2- thiohydantoin (82) (90 % yield) (Ware, 1950).



Subsequently, regioselective S-methylation yielded the imidazolone as depicted in scheme 21. It was also mentioned that displacement of the SCH_3 group by amines gave unsatisfactory results under non-extreme conditions; a modified procedure with tert-butylhydroperoxide (TBHP) was employed. This afforded leucettamine B (84 a) in 92% yield and N-benzyl leucettamine B (84 b) in 93% yield on using ammonia and benzylamine, respectively (Scheme 22) (Roue and Bergman, 1999).



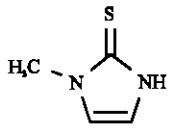
The reactions of methyl (or ethyl) isothiocyanate with dianions (85) which are readily derived from available cyclic thioureas with butyllithium, gave ring fused 1,3-disubstituted 1,3,5-triazine-2,4 (1H, 3H)-dithiones (87) and imidazolidine-2-thiones (86, 88) derivatives as reported by Noboru *et al.* (1986) (Scheme 23).



Scheme 23

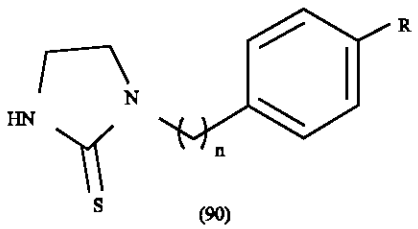
PHARMACEUTICAL IMPORTANCE

1-Methylimidazole-2-thione (methimazole) (89), a drug well known for its effective antithyroid activity, has been shown to be a potent inhibitor of the thyroperoxidase (TPO)-catalyzed iodination of tyrosine, or tyrosyl residues of thyroglobulin. It is readily oxidized to bis-[1-methylimidazole)] disulfide (Loksha *et al*., 2003).



(89)

A series of imidazolidine-2-thiones (90) and tetrahydropyrimidine-2-thiones were discovered as inhibitors of α-melano stimulating hormone (α-MSH) induced melanin production in melanoma B16 cells by Thanigaimalai *et al*. (2010). Primary bioassay showed that 1-(4-ethylbenzyl)-tetrahydropyrimidine-2(1H)-thione and 1-(4-tert-butylbenzyl)-tetrahydropyrimidine-2(1H)-thione exhibited potent inhibitory effect against α-melanostimulating h ormone (α-MSH) induced melanin production. As reported in the article cyclic urea containing compounds showed very weak activity as compared to cyclic thiourea deriatives (Thanigaimalai *et al*., 2010).



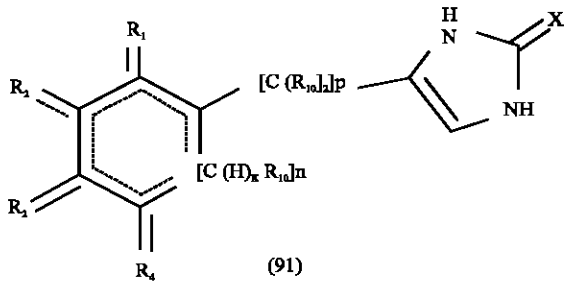
(90)

n = 1, 2 or 3
R = H, alkyl, alkoxy or Cl

US patent 4,642,351 describes a method for preparation of imidazolidine-2-thiones and imidazolidinone derivatives. It mentions the utility of N-substituted imidazolidinones and N-substituted 2-thionimidazolidinones as bactericides, central nervous system depressants, plant growth promoters and as female fly sterility agents (Gasch *et al*., 2000).

US patent 2004/0220402 describes 4-(substituted cycloalkylmethyl) imidazole-2-thiones, 4-(substituted cycloalkenylmethyl) imidazole-2-thiones, 4-(substituted cycloalkylmethyl) imidazol-2-ones and 4-(substituted cycloalkenylmethyl) imidazol-2-ones and related compounds (91) which are specific or selective to alpha$_{2B}$ and/or alpha$_{2C}$ adrenergic receptors in preference over alpha$_{2A}$ adrenergic receptors and as such have none or only minimal cardiovascular and/or sedatory activity and are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists of alpha$_{2B}$ adrenergic receptors (Chow *et al*., 2003).

US patent 2008/0091028 describes various substituted imidazole-2-thiones (91) which are useful as medicament in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists of alpha$_{2B}$ adrenergic receptors. They also have advantageous property that they have none or only minimal cardiovascular and/or sedatory activity and are useful for treating pain and other conditions like hypertension and depression (Chow *et al*., 2008).

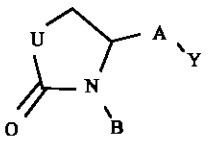


(91)

k is an integer having the vlues of or 1;
n and p have the values of 0, 1 or 2;
X is O or S

US patent 2007/0293551 describes substituted gamma lactams (92) as therapeutic agents. Methods, compositions and medicaments related to these compounds are also disclosed. The compounds disclosed are useful for the prevention or treatment of Glaucoma, preventing inflammation and pain in joint and muscle (e.g., Rheumatoid arthritis, Osteoarthiritis), Lung disorders, conditions of the gastrointestinal tract associated with

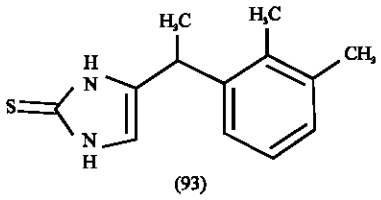
inflammation, Nephrotic syndrome, liver dysfunction, cancer, ischemic heart diseases etc. (Old, 2007).



(92)

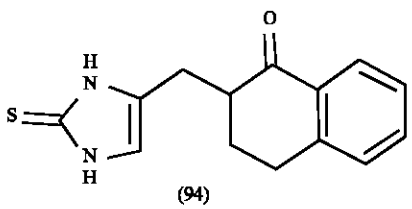
Where in Y = amide or ester, hydroxymethyl, ether, tetrazolyl, A = alkyl, alkene, alkyne, alkylaryl, heterocyclic ring, U = O, S, NR_1, where in R_1 is H, alkyl, acyl, benzoyl, biphenylacyl, sulfonyl, phenylsulfonyl, biphenylacyl, trifluoromethylacyl, or trifloyl; and B = aryl, or heteroaryl

US patent 2007/0004790 elaborates the use of 4-[1-(2,3-dimethyl-phenyl)ethyl]-1,3-dihydro-imidazole-2-thione (93) acting as an $alpha_{2A}/alpha_{1A}$ selective agonist. They can be useful in any of a variety of sympathetically-enhanced conditions such as migraines, gastrointestinal diseases like dyspepsia, psoriasis, tachycardias, Raynaud`s syndrome, scleroderma, metabolic disorders such as type II diabetes and in sexual dysfunction (Chow, 2007).



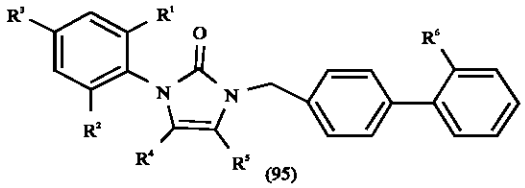
(93)

US patent 2006/0148872 describes 2-((2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)methyl)-3,4-dihydronaphthalen-1(-2H)-one(94) as agonists of $alpha_2$ adrenergic receptors; particularly as specific or selective agonists of $alpha_{2B}$ and/or to lesser extent $alpha_{2C}$ adrenergic receptors, in preference over $alpha_{2A}$ adrenergic receptors. Thus the disclosed compounds could be useful for treating conditions and diseases which are responsive to treatment of $alpha_{2B}$ and/or $alpha_{2C}$ adrenergic receptor agonists. Such conditions and diseases include but are not limited to, pain including chronic pain, neuropathic pain, corneal pain, glaucoma and other neurodegenerative diseases, diarrhea and nasal congestion (Chow *et al*., 2006).



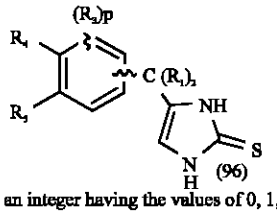
(94)

US patent 2004/0048911 describes a class of variously substituted 1-phenyl imidazol-2-one biphenylmethyl (95) compounds for use in treatment of circulatory disorders. Compounds of particular interest are angiotensin II antagonists. These compounds are particularly useful in treatment or control of hypertension and congestive heart failure (Reitz and Manning, 2004).



(95)

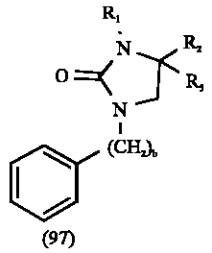
US patent 7,396,849 provides various 4-(condensed cyclic methyl)-imidazole-2-thiones (96) acting as $alpha_2$ adrenergic agonists. Several compounds of the disclosure are specific or selective to $alpha_{2B}$ and/or $alpha_{2C}$ adrenergic receptors in preference over $alpha_{2A}$ adrenergic receptors. Additionally some of the claimed compounds exhibited only minimal cardiovascular and/or sedatory activity (Heidelbaugh *et al*., 2008).



(96)

p is an integer having the values of 0, 1, 2 or 3

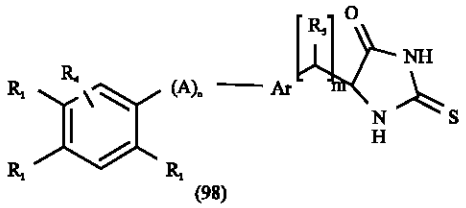
US patent 7,531,565 describes imidazolidin-2-one derivatives (97) and pharmaceutical compositions containing them and their use in the treatment of disorders and conditions modulated by the androgen receptor. Compounds described in the invention are useful for the treatment of prostate carcinoma, Benign Prostatic Hyperplasia (BPH), hirtutism, alopecia, anorexia nervosa, breast cancer, acne, AIDS, cachexia, as a male contraceptive and/or as a male performance enhancer (Lanter and Sui, 2009).



(97)

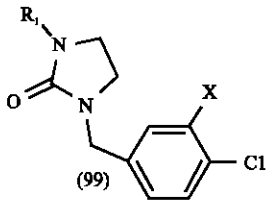
R_1 = H, alkyl etc., R_2 = alkyl, halogen substituted alkyl, hydroxy alkyl etc., R_3 = H, alkyl, aryl etc., R_4 = halogen, hydroxy, carboxy, nitro, amino, alkoxy etc.

US patent 6,974,826 provides insight into 2-thioxo-4-imidazolidinedione (98) derivatives which are useful in the treatment of diseases related to lipid and carbohydrate metabolism, such as type 2 diabetes, adipocyte differentiation, uncontrolled proliferation, such as lymphoma, Hodgkin's Disease, leukemia, breast cancer, prostate cancer or cancers in general; and inflammation, such as osteoarthritis, rheumatoid arthritis, Crohn's Disease or Inflammatory Bowel Disease (Pfahl *et al*., 2005).



(98)

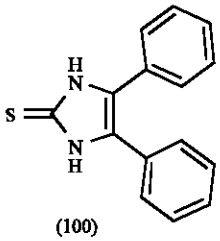
US patent 4,063,022 elaborates the (3,4-substituted benzyl)-2-imidazolidinones(99) as useful gastric acid antisecretory agents. The compounds described in the patent exhibit a salutary effect upon gastric acid secretion. Such effect is evidenced using a modified standard pylorus ligated secretory testing procedure in the rat (Schwan and Miles, 1977).



(99)

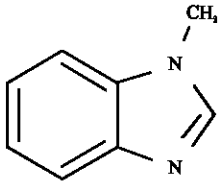
X = Cl or CF_3 and R = H or CH_3

A mevalonate derivative, containing 4,5-diphenyl-lH-imidazol-2-yl (100) moiety, as a pharmacophore was reported by Harris *et al*. (1992). It inhibits rat hepatic microsomal Acyl-CoA:cholesterol O-Acyl Transferase (ACAT) *in vitro* and thus has beneficial effects in the treatment of atherosclerosis (Harris *et al*., 1992).



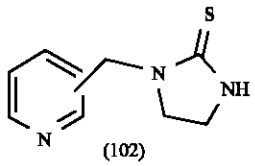
(100)

Derivatives of Imidazole-2-thione block reaction catalyzed by thyroid peroxidase (TPX) and closely related lactoperoxidase (LPX) and this property can be put to good use for the treatment of hyperthyroidism. The reactions of a series of benzimidazole-2-thione (101) with chemical and enzymatic oxidants were investigated by Doerge *et al*. (1993) to probe systematic mechanism of inhibition. Results obtained suggest that the substituted imidazole-2-thiones represent a new class of potential antihyperthyroid drugs that block TPX catalysed tyrosine iodination but do not cause irreversible enzyme inhibition (Doerge *et al*., 1993).



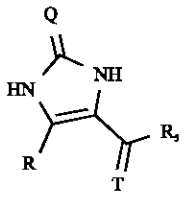
(101)

Isomeric 2-, 3- and 4-(pyridylmethyl) imidazole-2-thiones (102) were prepared by Ross *et al*. (1987). These compounds were shown to exploit the pH differential that exists across the chromaffin vesicle membrane and were shown to exhibit modest Dopamine β-Hydroxylase (DBH) inhibition *in vitro*. It also produced significant effects *in vivo* to increase the vascular ratio of dopamine to norepinephrine and to lower blood pressure (Ross *et al*., 1987).



(102)

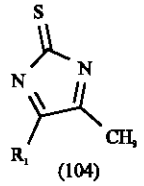
4-Methyl-5-substituted imidazole-2-thione (103) derivatives reduce the reperfusion injury that occurs when oxygen is reintroduced into the ischemic tissue as reported by Dage (1988). These compounds also reduced myocardial stunning, i.e., the prolonged loss of contractile function in the absence of necrosis after short periods of myocardial ischemia. Prevention or reduced reperfusion injury was observed with these derivatives when oxygen was reintroduced into the myocardium after a heart attack (Dage, 1988).



(103)

Q and T each independently are a divalent oxygen of suifur group; R_5 = H, alkyl; R_5 = aminoalkyl, substituted heterocyclic ring etc.

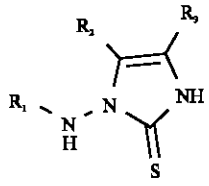
Smith and co-workers disclosed the use of 2-imidazolethiones(104) as antioxidants. The oxidation of ascorbic acid to dehydro-ascorbic acid was accelerated by metal ions such as copper. This stimulation of ascorbate oxidation was inhibited by the addition of 2-imidazolethiones and is proposed to complex copper through their potentially free SH groups (Smith and Gore, 1990).



(104)

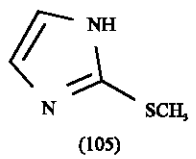
R^1 = H, alkyl, aryl etc.

A series of N-aminoimidazoline-2-thiones (5) and N-aminoimidazoles, with an uncommon spectrum of antiretroviral activity, were synthesized by Lagoja *et al.* (2003) and tested for their ability to inhibit the replication of Human Immunodeficiency Virus (HIV) and Simian Immunodeficiency Virus (SIV) in a cell culture model for acute infection. They were found to be potent inhibitors of HIV-1, HIV-2 and SIV replication in MT-4 cells acting mainly at the HIV- RT (Loksha *et al.*, 2003).



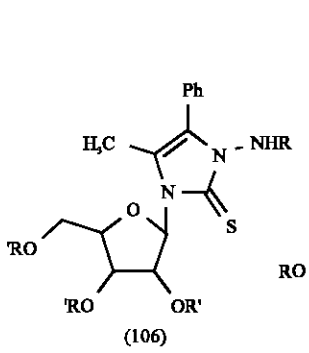
(5)

Copper(I) complexes of tri-o-tolylphosphine and heterocyclic thione ligands are reported to possess antifungal activity. 2-methylsulfanyl-1H-imidazole (105) derivatives showed activity against HIV-1 comparable to the activity of Nevirapine (Loksha *et al.*, 2003).

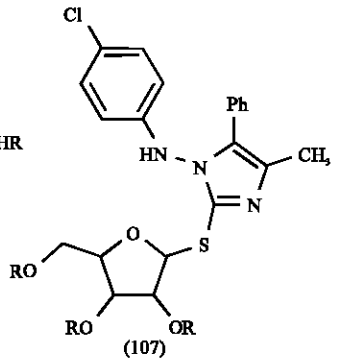


(105)

N-substituted 1-amino-2,3-dihydro-1H-imidazol-2-thione-N-nucleosides(106) and S-glycosides (107) have also been prepared and tested against HIV-1 and HIV-2 induced cytopathy in human MT-4 lymphocyte cells by Al-Masoudi *et al.* (2003).



(106)



(107)

CONCLUSION

Imidazolidine-2-thione or 2-one and imidazole-2-thione or 2-one derivatives exhibit various bioactivities which have intrigued scientists for decades to conduct research involving these ring system. Imidazole-2-thione heterocyclic ring containing drug, methimazole, is well known for its effective antithyroid activity and substituted imidazolidine-2-thiones are also reported to have very good antimicrobial and anti-HIV activities. This review has outlined such research approaches before focusing on the pharmaceutical utility of the said heterocyclic rings. A number of innovative synthetic techniques by means of conventional as well as by microwave irradiation techniques have been described in the synthesis of different derivatives of imidazole ring containing oxygen or sulfur heteroatom. Synthesis of different substituted thiohydantoins by liquid phase combinatorial chemistry to minimize the purification steps is also summarized in the article. With accessibility of such synthetic methods, scientists were able to synthesize numerous novel derivatives of imidazole heterocyclic ring containing oxygen or sulfur heteroatom.

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