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A comprehensive review article on mercapto-1, 2, 4-triazoles and their coordination properties

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1. INTRODUCTION

The increasing biological relevance of heterocyclic ring system involving nitrogen, sulphur and oxygen atoms offered us the prospect of exploring the capabilities of such systems to act as versatile compounds. The compounds such as alkaloids, antibiotics, essential amino acids, vitamins, nucleic acids, hemoglobin, hormones and many synthetic drugs and dyes contain heterocyclic ring systems. The delicious and appetizing flavour of many every day foods are heterocyclics. Many of the sensitizers used in photographic films, important constituents in plastic and resins are heterocyclics. The important analytical reagents such as *o*-phenanthroline and dipyridyloxine are heterocyclic compounds. Many of the promising cancer arresting, antitumour, antituberculosis, anti-AIDS, antiulcers, antiviral, antifungal and antibacterial drugs are heterocyclics.

2. BIOLOGICAL IMPORTANCE AND SYNTHESIS OF 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLES

Mercapto-1,2,4-triazoles are a group of compounds of clinical interest because of their wide spectrum of biological activities. The 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive and analgesic properties[1-5] .There is evidence that the antiviral[6] and antibacterial[7,8]activities of thiourea derivatives are due to the presence of –NH-C(S)-NH- function in the molecule and changes in the activity depend on the nature of its substituents.

A large number of 1H-1,2,4 triazole derivatives have been reported to possess activities such as fungicidal, herbicidal, anticonvulsant and plant growth regulators[9-11]. The disubstituted 1,2,4- triazole

derivatives were also reported to show antifungal, insecticidal and herbicidal properties which were similar to 1H-1,2,4-triazole derivatives[12-14] . The interest in these compounds further enhanced when it was shown that the 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically interesting drugs including H1/H2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, anti-anxiety agents, sedatives[15], anti-convulsant[16,17] and anti-inflammatory[18] agents . They have also been used in the gravimetric estimations[19] of silver, copper and gold.

The 4-amino-3-mercapto-1,2,4-triazole which possessed activity as weed killer[20] is the starting material for the synthesis of a wide variety of heterocyclic derivatives which are of great importance in medicinal chemistry[21,22]. The 1,2,4-triazole-3-thiones disubstituted in positions 4 and 5 were found to be useful as bactericides, fungicides and pesticides[23]. It has been reported that the amino triazolethiols undergo a cyclocondensation reaction with bromoacetyl-5-nitro furan to form the product which exhibited bactericidal activity[24]. The substituted 1,2,4-triazole nucleus is a part of marketed drugs such as fluconazole, terconazole, rizatriptan, alperazolame and triazolame[25-27].

A few 4-allyl / amino-5-aryl-1,2,4-triazoles were synthesized and tested for antibacterial and antifungal activity against Escherichia coli, Bacillus subtilis, Salmonella enteridis, Staphylococcus aureus, Aspergillusniger and Candida albicans[28]. Among the surface active agents containing heterocyclic moieties, some of the 1,2,4-triazole derivatives display diverse biological activity including antiparasitic, analgesic, antibacterial and anti-inflammatory activity[29-33]. The synthesis of these heterocyclic has received considerable attention in recent years[34-36] and find wide use in medicine, agriculture and industry[37].

The antimicrobial activity of the 1,2,4-triazole derivatives bearing long alkyl chain with sulfonic acid hydrophilic center[38] was determined in vitro using the hole plate and filter paper method[39].

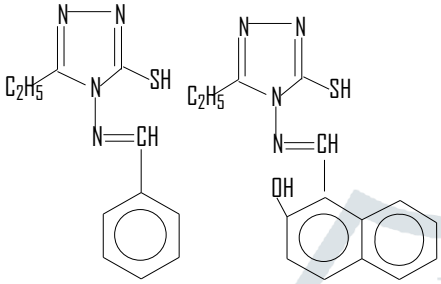
Joachim Goerdeler and Joachim Galinke have synthesized 3-mercapto-1,2,4-triazole by rearrangement of 2-amino-1,3,4-thiadiazoles[40]. Mercel Person et al synthesized 3-mercapto-1,2,4-triazole by the direct condensation of 4-aryl or alkyl thiosemicarbazides with esters in ethanol medium in the presence of alkaline condensation agents[41]. Later Hans Bayer et al[42] reported the preparation of 3-mercapto-1,2,4-triazole and its derivatives by reaction of thiosemicarbazide with respective aliphatic carboxylic acids followed by ring closure. Becker et al prepared 3-mercapto-1,2,4-triazole by heating halo substituted triazoles with nucleophilic reagents such as ammonia or amines and other reagents[20].

Eric Hoggarth reported the synthesis of 4-amino-5-phenyl-3-mercapto-1,2,4-triazoles[43].The potassium salts which were the intermediate compounds in the synthesis were obtained in high yields by stirring the corresponding hydrazide, CS_2, and a solution of KOH in absolute ethanol.

The Infrared spectral data was reported for oil suspensions of 1,2,4-triazole and some of its derivatives[44] . Bagal L.I investigated the basicity and structural relationship of some 1,2,4-triazoles, by the potentiometric titrations and by spectral methods[45]. Browne, E.J. &Polya, J.B. studied the IR spectra of N-substituted 1,2,4-triazoles[46] in the region of 1700-3000cm^{-1}, and classified according to the intensity and number of bands characteristic of strong inter-molecular hydrogen-bonding. Walter Freiberg et al recorded the NMR spectra of

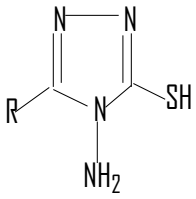
N-substituted 1,2,4-triazoles in 0.2M solution of $(CD_3)_2CO$ containing 1% tetra methyl silane as standard[47]. As expected the H-5 chemical shift was moved towards the lower field by electron withdrawing substituents and to higher field by electron donating substituents.

The 3-mercapto-1,2,4-triazole and 3-mercapto-5-methyl-1,2,4-triazole were used to stabilize solutions of acrylonitrile polymer against discolouration[48]. Yano Nobumitsu et al[49] synthesized the non-toxic nacreous pigments from 1,2,4-triazoles. The mercaptotriazoles resulting from 4-amino-3-ethyl-5-mercapto-s-triazole with benzaldehyde and 2-hydroxy-1-naphthaldehyde (**Fig. 1, 2**) have been reported[50].



(1) (2)

Patil S.A et al[51] prepared 5-mercapto-4-amino-3-substituted-1,2,4-triazoles and their mono and disubstituted derivatives. Jack Reid R. and Ned D. Heindel developed two improved methods for the synthesis of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles[52] (**Fig.3**). One of these involve the direct hydrazinolysis of potassium-3-aroyldithiocarbazates and the other involves ring opening and ring closure of 5-substituted-2-mercapto-1,3,4-oxadiazoles to the amino mercaptotriazoles. Both of these methods offer advantages over the classic Hoggarth synthesis[43].

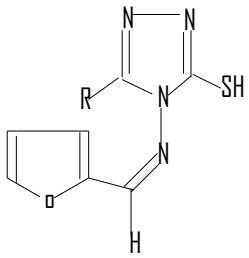


R=C_6H_5; *p*-FC_6H_4; *o*-BrC_6H_4; *o*-$OCH_3C_6H_4$; 4-pyridyl; 2-thienyl; cyclohexyl

(3)

Sudan et al synthesized various 3-substituted 6-(2',4'-dialkoxy-5-alkyl)-phenyl-5,6-dihydro-1,2,4-triazole [3,4-*b*]-1,3,4-thiadiazoles by the reaction of 4-amino-5- substituted phenyl-3-mercapto-triazole with aromatic aldehydes. The thiadiazoles were screened for anti-inflammatory, antifungal and antibacterial activities[53]. Eweiss N.F. et al reported the synthesis of a series of 4-amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives[54] which were found to exhibit a wide variety of biological and antimicrobial activities. Their study was aimed to correlate the antimicrobial activity of triazoles with different substitutions at the phenyl group in position-5. By masking either the amino or the mercapto group one at a time the group involved in the antimicrobial activity was demonstrated.

A number of 3-aryl-8-nitro-1,2,4-triazolo[3,4-*b*][1,3,4] benzothiadiazepines were prepared from 4-(2'-chloro-5'-nitro benzylidene amino)-5-aryl-3-mercapto 1,2,4-triazole. Their antifungal activity has been screened against Aspergillusniger and Helminthosporiumoryzae, were compared with that of fungicide carbendazim tested under similar conditions[55]. The Schiffs bases derived from furfuraldehyde condensed with 4-amino-5-mercapto-triazole and 4-amino-5-mercapto-3-alkyl-s-triazole[56] (**Fig. 4**) were reported

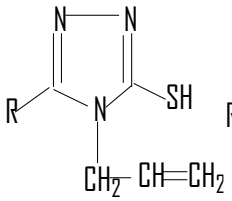


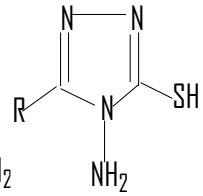
R=H; CH_3; C_2H_5; n-C_3H_7

(4)

Sasaki Norio et al[57] prepared triazoles and agrochemical microbicides containing them. The carbamoyltriazoles synthesized find applications as herbicides[58,59.] Wu Tai-Xing et al reported facile method for the synthesis of Schiff bases of 4-amino-5-hydrocarbon-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones with acetic acid as solvent and catalyst[60].

Panasenko O.J et al[61] synthesized the 1,2,4-triazoline-5-thione salts with amine and studied the interaction between their compositions and biological activity. The analgesic, diuretic and anti-inflammatory activities of these salts were also studied. A few 4-allyl/amino-5-aryl-1,2,4-triazoles with different substituents at position 4 of phenyl ring(**Fig.5,6**) were synthesized and studied for their biodegradability[28].

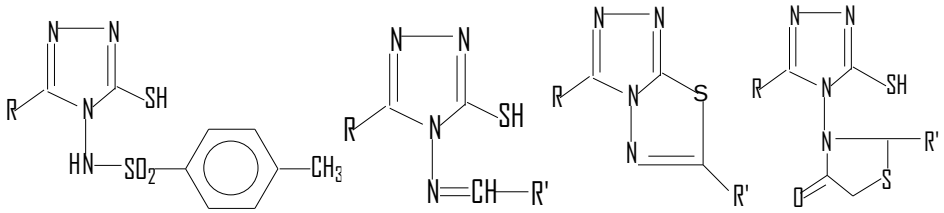




R= *o*-OHC_6H_4; *p*- OHC_6H_4; *o*-OH-*m*'-ClC_6H_3; *p*-$C_2H_5OC_6H_4$; *p*- OHC_6H_4CH2; *p*- $C_2H_5OC_6H_4CH_2$

(5) (6)

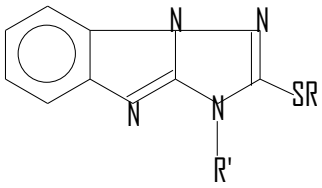
Refat El-Sayed reported the synthesis of a new series of biologically active 1,2,4-triazole derivatives bearing a long alkyl chain with sulphonic acid polar head groups **(Figs. 7-10)** in a single molecular framework[39]. These are expected to behave as anionic surface active agents possessing biological activity.



(7) (8) (9) (10)

R=$CH_3(CH_2)_{15}CHSO_3Na$; R'=CH_3; C_6H_5; *p*-ClC_6H_4; *p*-$OCH_3C_6H_4$

Some new derivatives of 1,2,4-triazolo[2,3-a]benzimidazoles (**Fig.11)** were synthesized through the reaction of 1,2-diaminobenzimidazole with CS_2. The resulting 1,2,4-triazolo[2,3-a]benzimidazole-2-thione intermediate reacted with one equivalent of the alkyl halide to give the corresponding 2-alkylthio derivatives[62].

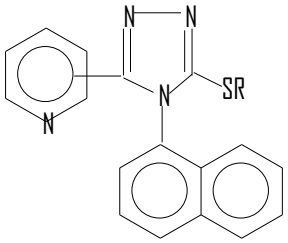


(11)

R=H; CH_3; C_2H_5; CH_2=$CHCH_2$; n-C_3H_7; i-C_3H_7; $C_6H_5CH_2$; $CH_2COC_6H_5$

R'=H; CH_3CO; C_6H_5CO; *p*-ClC_6H_4CO; *p*-$CH_3C_6H_4SO_2$

The synthesis of new 3-mercapto-1,2,4-triazoles bearing isomeric pyridyl and 1-naphthyl is reported using 1,4-disubstituted thiosemicarbazides in alkaline and acidic media respectively. The methylthio and benzylthio derivatives of the synthesized triazoles (**Fig.12**) are also reported[63].



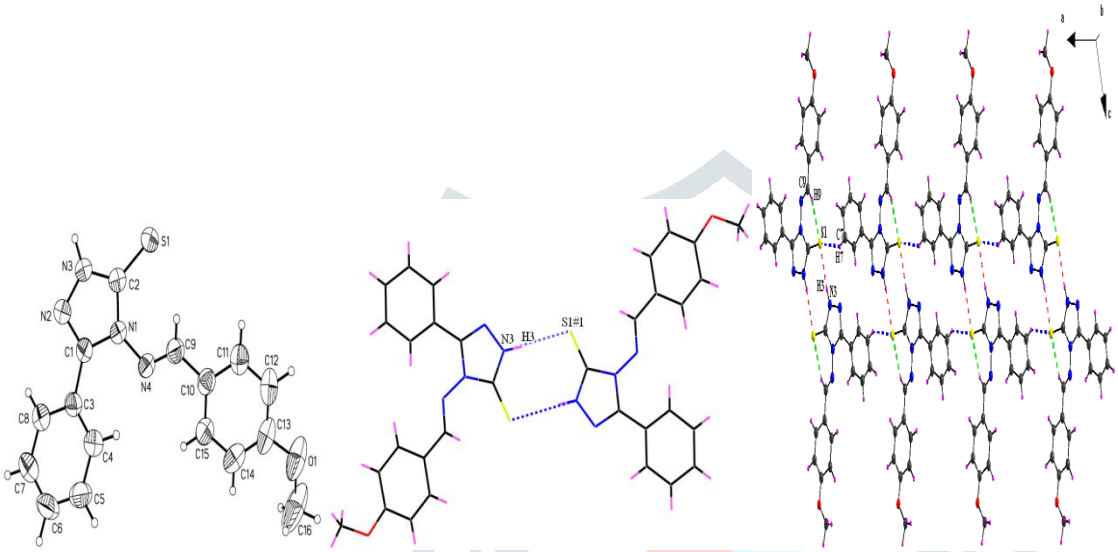
(12)

R=H; CH_3; -CH_2-Ph

In recent years S and N containing triazole derivatives have attracted more attention for their excellent corrosion inhibition activity. These compounds not only possess very high value of inhibition efficiency but also bring down the permeation current to a considerable extent[64]. In contrast to many commercial acid

corrosion inhibitors, which are highly toxic, most of the N- and S-containing triazole derivatives are environmentally benign corrosion inhibitors[65-67]

The compound 4-(4′-methoxy) benzylidene amino-5-phenyl-3-mercapto-1, 2, 4-triazole was synthesized and characterized by IR, NMR, Mass and XRD. The topological analysis of hydrogen bonds revealed the presence of both inter and intramolecular hydrogen bonding interactions. The participation of hydrogen on carbon in hydrogen bonding is evident from the present study. The QSAR properties are computed by Hyperchem 7.5 ′software and the antibacterial activity was evaluated .



3. COORDINATION CHEMISTRY OF 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLES

The metal complexes of transition elements with heterocyclic ligands especially those containing nitrogen and sulphur have diverse application in various fields including biology. Chelation therapy is the use of chelating agents to detoxify poisonous metal agents such as mercury, arsenic and lead by converting them to a chemically inert form that can be excreted without further interaction with the body. The chelation reduces the polarity of the metal ion because of the partial sharing of its positive charge with the donor groups of ligands. Such chelation increases the lipophilic character of the metal complex which is necessary to cross the permeability barrier of cells resulting in interference with the normal process of bacteria. Hence the complexes of many heterocyclic drugs prove as better chelating agents for the treatment of diseases. The interaction of transition metal ions with biological molecules provide one of the most fascinating areas of coordination chemistry.

The coordination compounds have found wide application in medicine for the treatment, management and diagnosis of diseases. Hence the antimicrobial, antifungal, antiviral, anticonvulsant, anticarcinogenic and antiherbicidal activities of thioamide ligands and its metal complexes are well known and gained more attention recently. The considerable research in the field of physiological activity of these compounds is due to their ability to chelate with metal ions. In the field of coordination chemistry their Schiff bases contribute, as an important class of ligands and their complexing ability containing different donor atoms is widely reported[68-71].

Antibacterial activities of some thiols and complexes have been investigated. The ligands and complexes were screened for their antibacterial activity against staphylococcus, Escherichia coli and Pseudomonas aero genes in the range of 25µg-500µg using serial dilution techniques[72,73]. The general trend of growth inhibition against all the bacteria is found to be in the order Ni(II) > Cu(II) > Co(II) > Zn(II). However all mercury complexes show more biological activity presumably due to highly reduced polarity of the metal ion which has strong affinity for sulphur. Metal complexes with thiols containing additional hydroxyl groups exhibit increased biological activity[74].

Mercaptotriazole reacts with Cu(II) in a 1:1 molar ratio to form CuC_2HN_3S[75]. The amperometric method was used to determine copper in steel. Birendra Kumar et al studied the complexingbehaviour of 1,2,4-triazole-3-thiol by synthesizing the complexes with Co(II), Ni(II), Cu(II), Ru(II), Rh(II), Pb(II), Pt(II) and Au(II). The metal chelates of 1,2,4-triazole-3-thiol with Zn(II), Cd(II), Hg(II), Tl(I) and Ag(I) were also prepared, and characterized on the basis of analytical and IR data. Hg(II), Cd(II), Zn(II) and Pb(II) complexes were tentatively assigned tetrahedral structures with polymeric intermolecular linkages through S and N atoms while Ag(I) and Tl(I) complexes are suggested to have polymeric linear structures[76,77]. .

Rao A.L.J. et al studied the polarographic behaviour[78] of sodium 1,2,4-triazole-3-thiolate in various supporting electrolytes. The reagent was successfully applied to the amperometric determination of Zn(II), Ag(I), Hg(II) and Tl(I) individually as well as in mixtures. The method was found to be simple, less time consuming and easily adaptable to micro determination of these metal ions as such or in some complex materials.

Takahashi et al reported that silver halide photographic material containing an infrared spectral sensitizer and a mercaptotriazole are capable of handling under room light[79]. Chen Xiapqing et al synthesized 1*H*-1,2,4-triazole-3-thiol resin (TATR)[80] and studied its sorption behaviour for platinum and gold ions. The structure of the resin was confirmed by elemental analysis, FT-IR and XPS.

Ashok Sen et al reported that two types of complexes of Co(II), Ni(II) and Cu(II) were formed with Schiffs bases derived from furfuraldehyde condensed with 4-amino-5-mercapto-triazole and 4-amino-5-mercapto-3-alkyl-s-triazole (alkyl=methyl, propyl)[56] . Zuchi F. et al investigated the inhibition of copper corrosion by1,2,4-triazole and some of its derivatives, such as amino, mercapto and carboxylic substituents[81].

Some of the substituted triazole compounds either alone or in combination with one or more therapeutically active compounds are used as sodium channel blockers to control sodium channel activity for decreasing various types of pains[82]. Due to their extreme volatility and solubility in non polar solvents, certain metal chelates are extensively used in the purification of metals[83].

The metal complexes of Schiff bases also have various industrial applications[84-86]. The metal binding properties of thiols were investigated fluorimetrically and spectrophotometrically using horse liver alcohol dehydrogenase as model metallo-enzyme. The steady state kinetics revealed that in the presence of the co-enzyme the primary interaction of a thiol with the enzyme is by thiolate competing with alcohol dehydrogenase

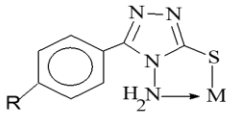
for the active zinc site[87]. The Co(II), Ni(II) and Cu(II) complexes of Schiffs bases derived from furfuraldehyde and different 4-amino-5-alkyl-3-mercapto-1,2,4-triazole derivatives were reported[59].

The synthesis and carbonic anhydrase inhibitory activity of metal complexes of 4,5-disubstituted-3-mercapto-1,2,4-triazole derivatives with Zn(II), Hg(II) and Cu(I) were reported[88]. 4-(4'-methoxybenzylideneamino)-5-methyl-4*H*-1,2,4-triazole-3-thiol (MBIMTT) has been evaluated as an extractant for rhodium(III) from variety of rhodium bearing materials and process solutions[89].

Bhargavi G. et al carried out equilibrium studies with 3-mercapto-1,2,4-triazole (MT) to determine the dissociation constant and formation constants of binary chelates with metal ions of biological significance. The studies indicated presence of one dissociable proton, corresponding to thiol group and formation of 1:1(ML) complexes[90]. Later 4-amino-5-(2'-hydroxy)phenyl-3-mercapto-1,2,4-triazole (AHPMT) and its Schiffs bases viz. 4-benzylideneamino-5-(2'-hydroxy)phenyl-3-mercapto-1,2,4-triazole (BHPMT) and 4-(2'-hydroxy)benzylideneamino-5-(2'-hydroxy) phenyl-3-mercapto-1,2,4-triazole (HBHPMT) were synthesized[91] in our lab. The effect of solvents on the dissociation constants of AHPMT, BHPMT and HBHPMT and stability constants of their metal complexes were studied by determining pKa and logK values of these ligands in 70% v/v acetone-water and dioxane-water media at 303K and 0.1M (KNO_3) ionic strength.

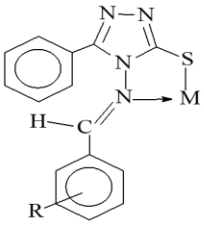
The synthesis and characterization of complexes of Ag(I), Tl(I), Zn(II), Cd(II), Hg(II), Co(II), Ni(II), Pd(II), Ru(II), Ru(III, Rh(III) and Pt(IV) with 4-(pyridine-2-carboxylidineamino)-3-mercapto-1,2,4-triazole have been reported. Octahedral structures have been proposed for the Co(II), Ni(II), Pd(II), Ru(II), Ru(III), Rh(III) and Pt(IV) complexes; square planar for the Pd(II) complex; tetrahedral for the Zn(II), Cd(II) and Hg(II) complexes and linear polymeric structures for the Ag(I) and Tl(I) complexes. The ligand coordinates to the metal ions through thiolsulphur after deprotonation and with nitrogen of the azomethine group[92].

The coordination properties of mercaptotriazoles and their derivatives were studied in both solution and solid state[93-96]. The stability constants were calculated from linear plots of log $(1-\bar{n})/\bar{n}$ VspL and log $(2-\bar{n})/(\bar{n}-1)$ VspL. The metal ligand formation curves data for APMT indicated the formation of 1:1 and 1:2 complexes except Pb (II) – APMT system wherein 1:2 stability constants are not obtained. The results with ANPMT reveal the formation of 1:1 complex in Ni(II), Cd(II) and Pb(II) –ANPMT systems and 1:1 and 1:2 complexes in Co(II) and Zn(II) –ANPMT systems . The $\bar{n}$ values of M(II)-BPMT, M (II)-MBPMT and M (II)-PMBPMT systems vary from 0.1 to 1.9 indicating formation of 1:1 (ML) and 1:2 (ML_2) complexes in all the systems except with Co(II) and Ni(II) where only 1:1 complexes are formed. The comparison of stabilities of APMT with BPMT reflects the order of pKa value of APMT and BPMT, wherein the effect of change of hybridization in APMT at one of the nitrogen atom from sp^3 to sp^2 in BPMT is attributed for the observed trend. Further the higher stabilities of MBPMT and PMBPMT than BPMT is due to the electron releasing effect of methyl and methoxy group at para position of the ring, thus reflecting the +M effect in MBPMT and PMBPMT. The results reveal that APMT, ANPMT, BPMT, MBPMT and PMBPMT are S and N donor ligands with one dissociable proton and forms five membered chelate rings with metal ions Figs A& B.



R= H, APMT
R= NO_2, ANPMT

Fig A



R=H, BPMT
R=p-CH_3, MBPMT
R=p-OCH_3, PMBPMT

Fig B

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