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Review .Theoretical study of synthesis and pharmaceutical study of Tetrazine derivatives

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ABSTRACT

Tetrazinesareheteroaroaticcompoundswithfournitrogensinasix membered ring similar to that of benzene. There,, are three majorisomers,1,2,3,4-tetrazinee,1,2,3,5-tetrazinee,and1,2,4,5tetrazinee,dependingontheplacementofnitrogensinthering,with1,2,4,5-tetrazine being the most prevalent. Tetrazine synthesized by different pathways , Tetrazine application as Antibacterial, antifungal, anticancer, antiviral, antimalarial, and antimicrobial activities are found in several tetrazine compounds. Some hexahydro-s-tetrazines are good analgesics and anti-inflammatories, while 3- arylamino-6-benzylamino-1,2,4,5-tetrazines exhibit significant antimalarial activity. A number of tetrahydro-s-tetrazines have been shown to have antibacterial and antifungal properties, with several 1,4-dihydro-s-tetrazine derivatives possessing antiviral and anticancer properties.

1.INTRODUCTION

thefirstreportofs-tetrazineattheendofthenineteenth century as Pinner°published. He made numerous s-tetrazines but didn't do muchmoreresearchintotheirproperties.Scientistshavebecomeincreasinglyinterested in the chemistry of s-tetrazines throughout the years. Manynew s-tetrazines derivatives, including symmetrical and unsymmetricaltetrazines, havebeen producedinavarietyoftechniques.Tetrazinesareheteroaroaticcompoundswithfournitrogensinasixmembered ring similar to that of benzene. There,, are three majorisomers,1,2,3,4-

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tetrazinee,1,2,3,5-tetrazinee,and1,2,4,5 tetrazinee, dependingontheeplacementofnitrogensinthering,with1,2,4,5-tetrazine being the most prevalent. The three isomers, as well as theatomnumbering,aredepictedinFig 1 [1]

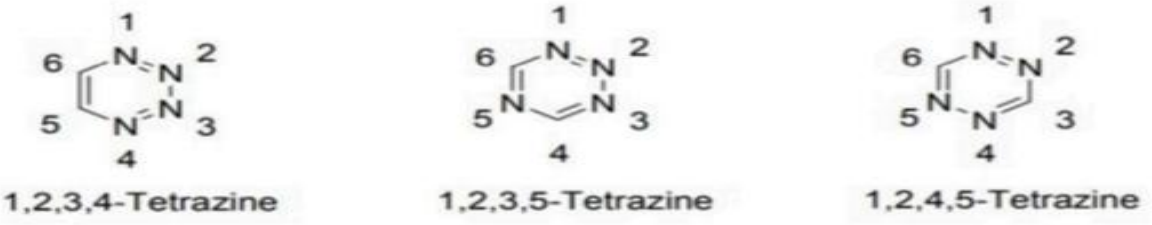

Figure No 1:Tetrazine isomer structure

Because of its electron<poor polyhetero cyclic aromatico character, which isalso proceed amenablee to click chemistry, the s-tetrazine (Tz) unit is of greatinterestinphotophysicsandforbiologicalapplications.Diversificationofsyntheticapproachesforconceivingnewtetrazinecompoundshasproven to be quite beneficial in expanding present uses. The effectivesynthesisofrestrictedbistetrazineswithanovelbridgeclamppstructure was recently reported using a coppercatalyzedhomocouplingtechnique[2].

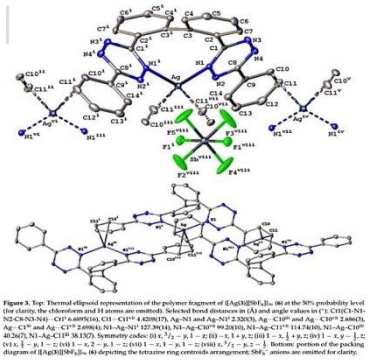

Figure No 2: coppercatalyzedhomocouplingtechnique

The greatest distinguishing feature of tetraziness is their strong affinity of electronnn, which derives from the replacement of four CH groupss on thearchetypal aromatic ring with four additional electronegative nitrogenatoms. They are, in fact, the most electron-poor C-N heterocycles12-15,and asaresult, theyarereduceddathighto thevery

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yhighpotentialss(-0.8 0.4VvsAg+/Ag).Tetrazine'sotherdistinguishinggfeatureisitslow-lying*orbital,whichresultsinann-*transitioninthevisiblerange.[3]

BecauseoftheirenormouspotentialasemissivelayersandconstructingsensorsFluorescenceeandreversibleeelectro activityareparticularlyxfascinatingfeaturesinthisregard,becausefluorescentand/or electro activemoleculess can be quenchedd in a short period oftime,resultinginsensingcomponentsthataredependentonthequenching agent. For this aim, the tetrazine family appears, to be a verypromisingg and exciting class of compoundd. They're reversibly electrical lyactiveheterocycleswithalotofcolor.Theyshowthefollowinginformation[4].

They have a strong electron affinityy,,, making them reduciblee at high toveryhighpotentialss(infact,theyareamongtheelectronpoorestheterocycles), and they have a low lying *orbitall, resulting in an n-*transitioninvisiblelightt.Furthermore,alltetrazinefamilycompounds are fluorescent in solutionn as well as in the crystalline state.Thischaracteristicplacesthemamongthetiniestcrystallineorganicfluorophoress yet synthesized in the visible region, and so makes particularlythemmPotentialsensoruses makeitappealing as showen in figure No 3 [5].

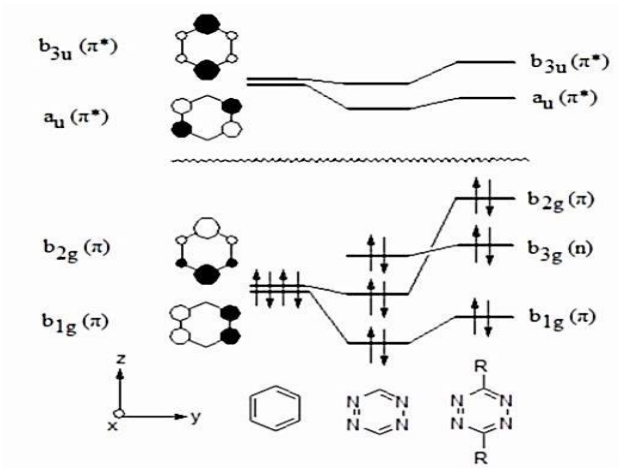

Figure No 3: *transition of of electron of tetrazine

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shifts The energy of the border orbitals of benzene and stetrazine as aresultof1,2,4,5-tetraazaireplacementand3,6-disubstitutionbydonatingelectrongroupss Rare depictedinthisqualitativegraphic.The1,2,3,4-tetrazineand1,2,3,5-tetrazinesystemshavebeenthesubject of theoretical computations. Of the three potential tetrazines,the1,2,4,5-tetrazinesystemisthesolestableisomerr.The1,2,4,5-tetrazine isomer has been the subject of the majority of theoreticalstudies.Acomputerinvestigationofthestability,energy of homodesmoticstabilization, electron distribution, and magnetic ring current oftetrazines waspublishedby FabianandLewars[6].

1 , 2, 4, 5-Tetrazine compounds have a strong biological potential, withantiviral,antifungal,anti-inflammatory,andanticancereffects.Furthermore, these chemicals have long been employed as pesticidesandherbicides[7].
It's also been employed as a peptide bondbinder recently in the synthesis of aminoacids.Inthispresentation,1,2,4,5-tetrazines were synthesized from a uniquecompoundknownasthiocarbohydrazide,which has very a wide range of applicationss inheterocyclicchemistry.Itiscommonlyusedasagoodsynthontoformvariousheterocyclic compounds such as triazoles,thiadiazoles,andtetrazines.Infact,thiocarbohydrazide was once employed tomakeaspecificsortoforganometallicchemical.Furthermore,itdemonstratedantibacterial,antitumor,antifungi,andexcellentdrugusesintheindustrialandbiologicalfields as showen in figure No 4, structure of 1,2,4,5-Tetrazine [8].

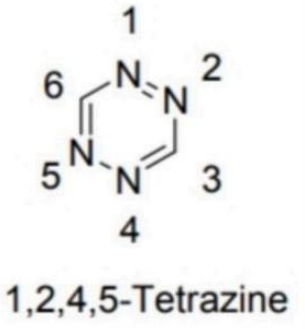

Figure No 4: structure of 1,2,4,5-Tetrazine

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2.Synthesis of tetrazine :

1 - Dr. PavelAnzenbacher Jr. Adviser al et. developed (3,6-Dihydrazino-1,2,4,5-tetrazine)asananionsensorbycombining(3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine)withhydrazinehydrate as showen in Scheme No1 [9]

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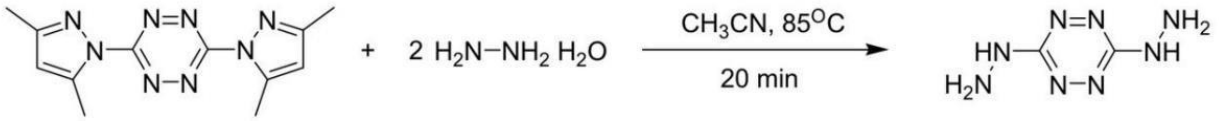
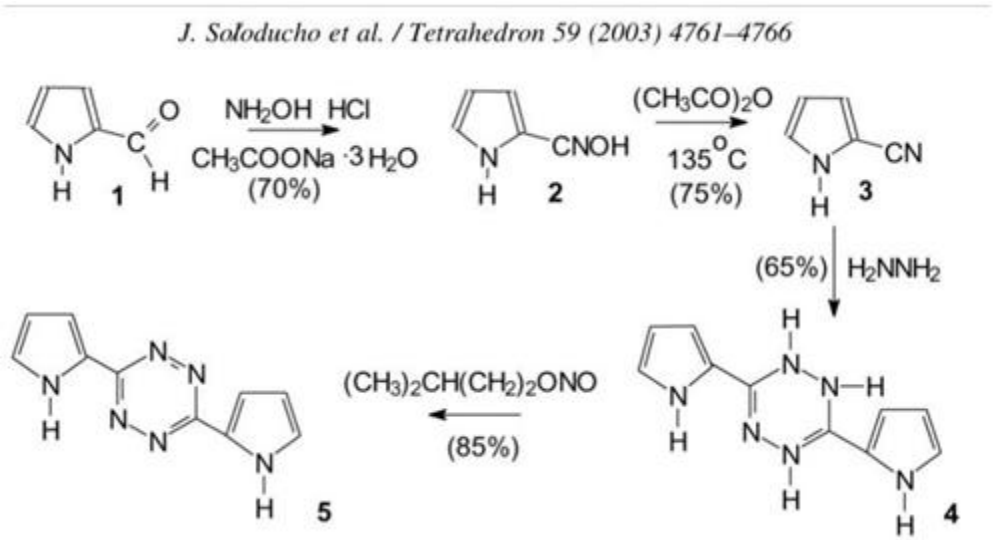


Scheme No1: Dr. PavelAnzenbacher Jr. Adviser al et. method

The above reaction carried in presencee of 150 mL of acetonitrile,andthemixturewasthenrefluxedfor20minutes.Aftercoolingtoroomtemperature,themixturewasfilteredandwashedwithacetonitrile.

2- The author JacekDoskocz et al. produced 3,6-bis-(pyrrol-2-yl)-1,2,4,5-tetrazineeasameterialfor electropolymerazation [10]



Scheme No2: author JacekDoskocz et al. method

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by reacted 2-pyrrolealdehyde hydroxylaminee hydrochloride and sodiumacetatee to yield 2- pyrrolealdoximee (Synthesis of 3,6-bis-(pyrrol-2-yl)-1,2,4,5-te The equivalent nitrile was obtained by treating component 2with an excess of anhydride of acetic (3). 8 Tetrazine was reacted with 2-pyrrolenitriletoproducenovel3,6-bis(pyrrolyl)-1,2-dihydro-1,2,4,5-ttetrazine.4.Compound4wasoxidizedtothefullyaromaticcompound afterreactionwith isoamylnitrite [11] .

3-The authorFARAGM.A. ALTALBAWYet al. Has beensynthesized(triazolo[4,3-b][1,2,4,5]tetrazinee)Asantifungalandantibacterial as showen in scheme No3 : FARAGM.A. ALTALBAWYet al method [12].

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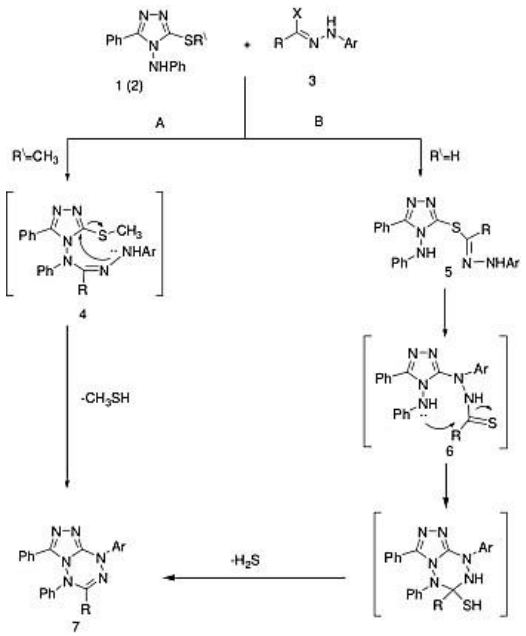

Scheme No3 : FARAGM.A. ALTALBAWYet al method

4-The author A.Y.Hasssanetal.Hass Has beencreatedsynthetically6-(4-chloro-phenyl)-3-trichloromethyl-5,8dihydro[1,2,4,]TRIAZOLO[3,4-B][1,3,4,]THIADIAZOLE-6(5H,)DIHYDRO-[1,2,4]-THIONE,5,8-TRIAZOLO[4,3-B,][1,2,4,5,] Byreacting with TETRAZINE, it can be used as an anticanceragent.3-Hydrazino-5-trichloromethyl-[1,2,4]InalcoholicKOH,combinetriazol-4-

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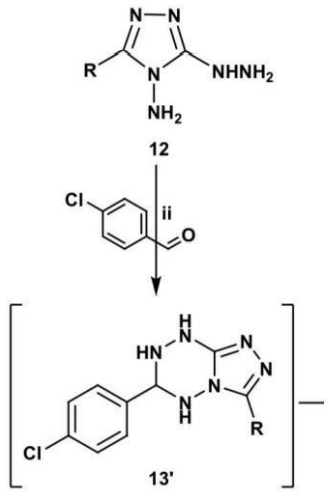
ylaminewithparachlorobenzaldehyde.Afterallowingthereactionmixturetocool,itpouredontocrushediceandscratched.Thesolidwasthenfilteredoutandrecrystallizedinacetone as showed in a scheme no 4[13].



Scheme No4 : author A.Y.Hasssanetal method

5-TheauthorBassamAHassanhasbeensynthesized.HEXAHYDRO-3,6-DIPHENYL-1,5,6,7,8,8A-DIPHENYL-1,5,6,7,8,8A-DIPHENYL-1,5,6,7,8,8A-D [1,2,4]TRIAZOLO[4,3-

B,][1,2,4,5,]TETRAZINEeasanantibacterialagentItmadebyreactingbenzohydrazidewithKOH,CS2,andHydrazinehydratetoproduce4-amino-5phenyll-4H-1,2,4-triazole-3-thioll(I)then3-hydrazine-5-phenyl-4H-1, 2,4-triazole-4-amineis formed when amixtureeofproducedcompounds(I)reactswithhydrazinehydrateinpyridine(II).Thereaction ofcompound(II)withbenzaldehydeinalcoholicKOH yields 3,6-diphenyl-1,5,6,7,8,8-a-hexahydro-1,5,6,7,8,8ahexahydro-1,5,6,7,8,8a-hexahydro-1,5,6,7,8,8a-hexahydro-1,5,6,7,8,8a-hexa[1,2,4]triazolo[4,3-b][1,2,4,5]tetrazine(III) as showed in scheme No 5 [14-31] .

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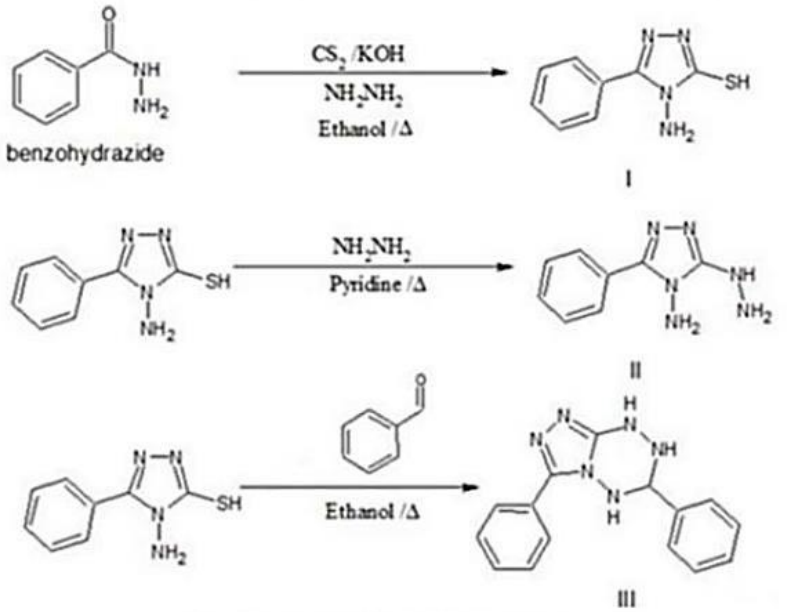

Scheme 1 : Synthesis of triazolestetrazine.

Scheme No 5 : synthesis of traizoletetrazine.

3.Applicationoftetrazine

Antibacterial, antifungal, anticancer, antiviral, antimalarial, and antimicrobial activities are found in several tetrazine compounds. Some hexahydro-s- tetrazines are good analgesics and anti-inflammatories, while 3- arylamino-6- benzylamino-1,2,4,5-tetrazines exhibit significant antimalarial activity. A number of tetrahydro-s-tetrazines have been shown to have antibacterial and antifungal properties, with several 1,4-dihydro-s-tetrazine derivatives possessing antiviral and anticancer properties.

3.1 Antibacterialeffects:

Both Gram-negativee and Gram-positivee bacteria were used to assess the activity antibacterial of the produced heterocyclestetrazinee compounds. When compared to the tetracyclinee utilized as aantibiotic referencee, the inhibition zoneeagainst the growth of the verifiedd bacteria for several tetrazine compounds demonstratedoutstanding antibacterial efficacy against all the tested bacterial strains. In the aromatic system, the

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ortho-, meta-, or para-positionn of the electron-donating groups a consider impact on bioactivities. Furthermore, the presence of heteroatoms such as oxygen [O], [S]sulfur, and [N]nitrogen plays an important impact in the antibacterial activity reported. Sulfur-containing chemicals may also hinder enzyme formation, as enzymes require certain groups for their action and are particularly vulnerable to deactivationn by the substances[32].

3.2 Anticancereffects:

Patients with chemotherapy-resistant malignancies are being pushed to create novel medicines due to a dearth of treatment choices. 1,2,4,5-tetrazine derivatives are a class of heterocyclic chemicals with anticancer activity across the board. We developed and tested two new seriess of 3,6-disubstituted-1,2,4,5-tetraziness in four cancer cell lines (H1975, HL-60, HCT116, and HeLaa) as well as Vero cellss. Our findings suggest that chemical modifications in the aromatic moiety can alter cytotoxicity and selectivity in a favourable way. In various cancer cell lines, these compounds were found to be more effective than the medicines etoposide and vatalanib, as well as more selective when compared to Vero cells. In silico investigations using the 3D-QSAR analysis validated preliminary data about some structure-activity correlations [33].

3.3 Treatmentfortuberculosis:

The antibacterial and anti-tumor properties of imidazo[1,2-b][1,2,4,5]-tetrazines are well documented. Some members of this class have recently been discovered to be inhibitors of serine-threonine protein kinases, which can be utilized to treat drug-resistant tuberculosis [17]

3.4 Electopolymerization:

The synthesized and production of new conjugated polymerss as low-cost materialss with significant promise for electrical and optoelectronic applicationss has gotten a lot of interest in recent decades. We published a paper on the synthesis of 1,4-bis(pyrrol-2-yll)aryleness a few years ago. 3–5 The synthesis of derivatizedd, possibly soluble, and processablepyrrole-containing polymerss is now possible thanks to this new synthetic

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method[34].

3.5 Otherapplication:

Thetetrazine-alkeneligationhasbeenusedfor ,imagingbiomoleculeslikeproteinsandDNAlncells ,Imagingtumorsinliveanimalsandforprodrugactivation[35].

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