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Research Article

Biological Properties of Triazole Derived Compounds and Chalcone Complexes

Sachin KhushalraoKhuje*[1], Jagdish Chand Pati[2], Manmeet Singh Saluja[2]

[1]Research Scholars, Department of Pharmacy, SunRise University, Alwar, Rajasthan.

[2] Research Supervisor, SunRise University, Alwar, Rajasthan.

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Corresponding author: Sachin KhushalraoKhuje

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Abstract:

Synthetic organic chemists benefit greatly from modern efficient methods for the synthesis of azole derivatives. **T**he main aim of the study is Biological Properties of Triazole Derived Compounds andChalcone Complexes**.** The Analar grade reagents and solvents were utilized in all experiments. Chloride salts of all metals were used.After the experiment, we were able to obtain and characterize the desired molecules. Their screening revealed that chelation or coordination increased the antibacterial and antifungal activities. In this research, we concentrate on creating a novel family of phosphorus-based ligands attached to 1,2,3-triazole. We present the synthesis and characterisation of ligands, and we investigate their reactivity with many different transition metal derivatives.

Keywords: Synthetic, Chelation, Triazole, Metal, azole, Anti-bacterial, Anti-fungal,Chalcone

Introduction

An overview of azoles (Fig.1.1) and their significance in medicinal chemistry is provided in this chapter. 1, 3 Many pharmaceuticals, bioactive compounds, and natural products include azoles as an essential heterocyclic component. Synthetic organic chemists benefit greatly from modern efficient methods for the synthesis of azole derivatives.

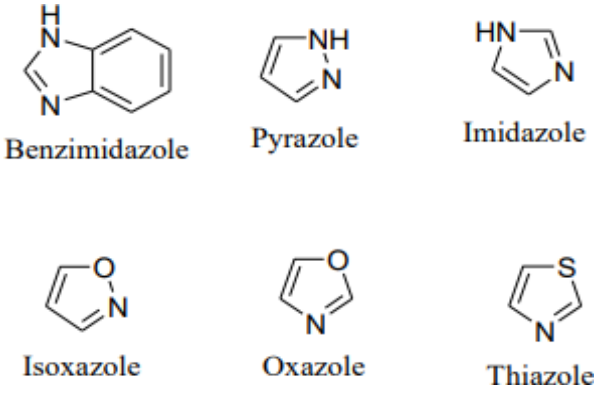


Fig.1.1: Azoles

Nitrogen heterocyclic ring compounds with at least one additional non-carbon element, such as nitrogen, sulphur, or oxygen, are known as azoles. The original molecules feature two double bonds and are aromatic; from there, one may derive a series of progressively smaller analogues (azolanes and azolidines). Each heteroatom in the azole ring contributes exactly one lone pair of electrons to the aromatic bonding. When azoles are reduced, their names keep their prefixes (for example, pyrazoline, pyrazolidine). In azoles, the ring atoms are numbered beginning with the heteroatom that is not involved in a double bond. Many azoles are utilized as antifungal medications because they block the production of ergosterol (a vital component of the fungal plasma membrane) by the enzyme 14-demethylase in the fungus.

Biological Activity Azole Derivatives

Benzimidazole, an azole molecule, was initially reported to have antifungal action in 1944 by Woolley, who was investigating the effects of biotin shortage in animals and microorganisms. He pointed out that biotin and purines had structural similarities to benzimidazole, but that biotin was unable to counteract the drug's biological effects, but the purines adenine and guanine were. Woolley's original finding was largely dismissed since mycotic infections were of little interest in 1944, but his results were verified in 1949. After 30 years, Vanden Bossche noticed that another azole moiety with antifungal action, phenethyl imidazole, interfered with the absorption of purines in yeast from Candida spp. The work of Woolley was resurrected in 1952 when Jerchel et al. revealed the considerable antifungal activity of several substituted benzimidazole compounds. This study prompted other researchers to examine this class of compounds for potential antifungal therapeutic use. Chlormidazole, a chlorobenzyl imidazole, was produced and evaluated in clinical trials for the first time in 1958–1959.In the beginning, there was chlormidazole, the first azole derivative to be produced and commercialized as an antifungal medicine.

Overview of Heterocyclic Compounds:

All or most of the atoms in the molecules of heterocyclic compounds, also known as heterocycles, are connected in rings that include at least one atom of an element other than carbon (C). The prefix hetero- designates any atoms in the ring that are not carbon, while the cyclic component of heterocycles denotes the existence of at least one ring structure. While carbon remains the most common ring atom in heterocyclic compounds, there has been a steady expansion of this field to encompass compounds with a wider variety of heteroatoms in their rings.

To the untrained eye, heterocyclic compounds like cyclopropane (with three-carbon atoms in the ring) and benzene (with six-carbon atoms in the ring) are virtually indistinguishable from their all-carbon ring analogues. However, the presence of the heteroatoms gives heterocyclic compounds physical and chemical properties which might be regularly pretty exceptional from those of their all-carbon ring analogues. Many of the biological building blocks necessary for life are found in heterocyclic molecules. Nucleic acids, which transmit hereditary information, are composed of lengthy chains of heterocyclic devices bound together by a variety of chemical and physical forces. Heterocyclic compounds include the majority of hallucinogens and many naturally occurring colours, vitamins, and medicines.

Literature Review

S.Jubie, P.Sikdar, R. Kalirajan,B. Gowramma, S.Gomathy, S.Sankar,K. Elango, [2011] developed several new

ciprofloxacin analogues as antibiotics by chemical synthesis. Mannich reaction has been used to integrate ciprofloxacin into a novel family of 1,2,4-triazole Schiff bases. Antimicrobial activity of the novel compounds was tested in vitro at a 10 g/ml concentration against B. subtilis, K. pneumoniae, and P. aeruginosa. The in vitro gram-positive and gram-negative activity of all of the compounds was either on par with or even somewhat higher than that of the standard ciprofloxacin. Twenty-eight 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazole derivatives were synthesized by Bijullakshman, and there in vitro efficacy against Rhizoctoniasolani, Sclerotiumrolfsii, Fusariumoxysporum, Pythiumaphanidermatum, Puccinia recondite, and Bipolarissorokiana was evaluated.

Tomasz Plech et al. [2011], Some 1,4-disubstituted thiosemicarbazide compounds were synthesized rapidly and effectively, as disclosed. Thiosemicarbazide derivatives were produced in high yields from the reaction of 3-chlorobenzoic acid hydrazide with a variety of aryl isothiocyanates. Compounds with a 1,2,4-triazole ring were produced by cyclization in the presence of 2% NaOH. In addition, a group of novel Mannich bases with 1,2,4-triazole-like structures has been synthesized. The effect of substituent type and location on the antibacterial activity of the compounds reported was explored. New s-triazoles and Mannich bases were also synthesized. Especially against Gram-positive bacteria, certain compounds shown encouraging antibacterial efficacy.

Aniket Kshirsagar,M.P.Toraskar et al. [2012] synthesized Schiff's bases of 5-mercapto-3-(3-pyridyl)-4H-1,2,4-triazole-4-yl-thiosemicarbazidebymicrowaveassistedmethod.Thesynthesizedcompoundshavebeenevaluatedinvitrofortheirantibacterial,antifungaland anticonvulsantactivities.

R.K.Malietal.[2019]Using Fluconazole as a standard, we synthesized 5-(N-substituted carboxamidomethylthio)-3-(3'-pyridyl)-1,2,4-triazole and tested its antifungal and antitubercular activity at 50 and 100 g/mL against Candida albicans and Aspergillusniger, respectively. A series of new coumarin based 1,2,4-triazoles were synthesized and evaluated for antimicrobial activitiy in vitro against Gram-positive bacteria (Staphylococcus aureus, MRSA, Bacillus substilis and micrococcus luteus), and Gram-negative bacteria (Escheichia coli, Proteus vulgaris, Salmonella typi and Shigelladysenteriae) as well as fungi (Candida albicans, Sacchoromycescerevisiae and Aspergillusfumigatus) by two-fold serial dilution tehniques.

An Anees Siddiquietal.[2011]I've produced some 4-[1-(aryl) methylidene-amino] Starting with isonicotinic acid hydrazide, potassium hydroxide, and carbon disulfide, we synthesized 3-(4- pyridyl)-5-mercapto-4H-1,2,4-triazole and tested it for analgesic and antipyretic effects. Rats given 25 mg/kg were tested for analgesic effects using the tail-flick technique, and antipyretic effects were tested using Brewer's yeast-induced pyrexia. The rectal temperature was taken using a clinical thermometer after a 20 ml/kg dose of a 20% aqueous solution of Brewer's yeast in normal saline was injected subcutaneously below the nape to produce fever. The antipyretic effect of several substances was compared to that of aspirin (300 mg/kg).

Research Methodology

1, 2, 3-triazole-chalcone hybrids have action against prostate cancer cell lines, as indicated in Fig 1.2.

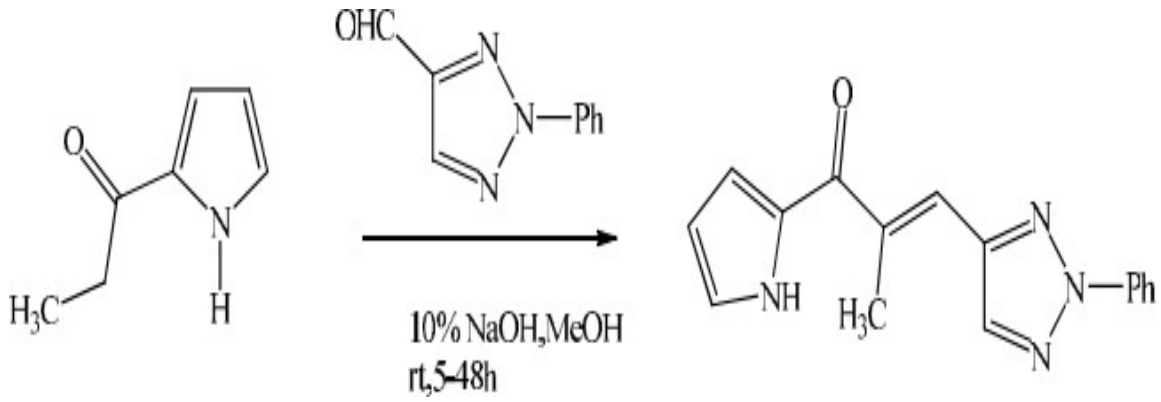


Fig1.2: triazole chalcone hybrid.

PREPARATION OF 4H-1, 2, 4-TRIAZOLE-3-CARBALDEHYDE

DMF (7.3093 g, 7.71 ml, 0.10 mol) is put in a 500 ml three-necked round-bottom flask equipped with a dropping funnel and reflux condenser. The flask is placed in an ice bath and kept at 10- 20oC, and after 15 minutes, an exothermic reaction begins with the production of a 'phosphoryl trichloride dimethyl formamide' complex when 0.10 mol of POCl3 (15.3332 g, 9.32 ml) is introduced via the dropping funnel. After 15 minutes of stirring in the ice bath, the liquid is ready to be used. After lowering the temperature of the mixture to 5oC by adding 25 ml of ethylene dichloride (C2H4Cl2) and stirring it for 1 hour, the triazole solution (6.7089 g, 6.93 ml, 0.10 mol) is slowly added through a dropping funnel. After the addition is complete, the ice bath is swapped for a heating mantle, and the mixture is agitated for 15 minutes while maintained at a temperature that causes HCl to evolve. The mixture is cooled to 25-30 °C, and then 75.0 g of CH3COONa.3H2O is added, drop by drop at first, and then as quickly as possible, via the dropping funnel. For another 15 minutes, keep the reaction mixture on a low simmer with constant, vigorous stirring. The cooled liquid is separated into C2H4Cl2 and water using a 1 litter separating funnel. Three times with roughly 50.0 ml of ether, the aqueous phase is extracted. Three 10.0 ml portions of a saturated aqueous Na2CO3 solution are added constantly at initially to the combined ether and C2H4Cl2 solutions in an effort to slow down the CO2 evolution rate. After distilling out the solvents, the residual liquid is transferred to a Claisen flask and distilled at decreased pressure in an oil bath. As an almost white liquid that quickly crystallizes, the yield of crude 2-formyl triazole is 0.80 g. Procedure for obtaining pure aldehyde from the crude product is given in Fig 1.3. The crude product is dissolved in boiling petroleum ether (b.p. 40-60oC) in the ratio of 1 gm of crude 2-formyl triazole to 25 ml of solvent, and then the solution is cooled slowly to room temperature, followed by refrigeration for a few hours. Shade: pure white (69.25%) yield, (78-79% literature), (60-80° literature) melting point of (48°).

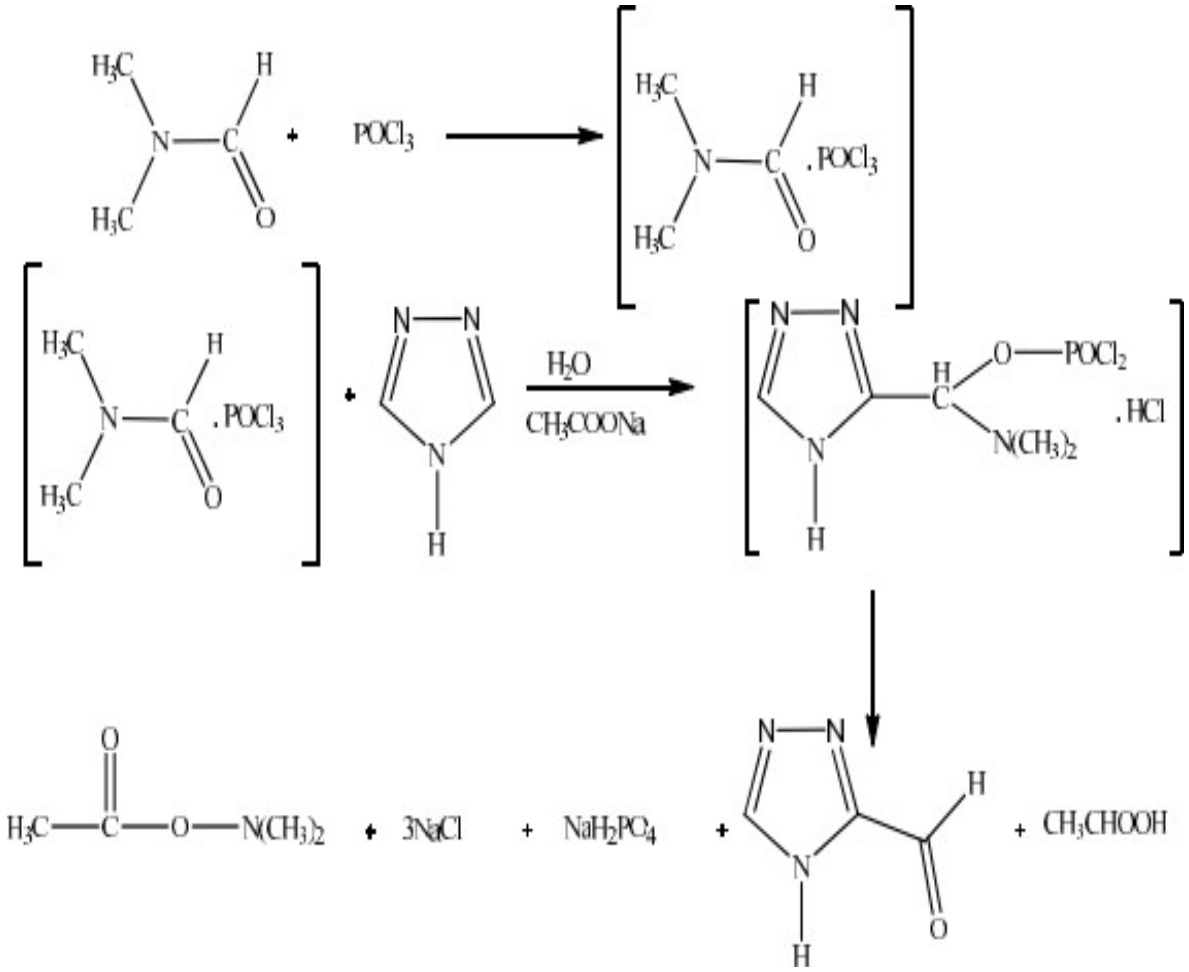


Fig1.3: Preparation of 4H-1, 2, 4-triazole-3-carbaldehyde.

DATA ANALYSIS

SYNTHESIS OF 1, 2, 4-TRIAZOLO-CYCLOHEXANONE DERIVATIVES: A GENERAL PROCEDURE

Fig 1.4 details the chemical steps required to produce the triazole-substituted chalcone derivatives (1g-1j). For 30 minutes, the 40 ml of ethanol was mixed with 2 formyl/2,4-acetyl triazole derivative on ice. Drop by drop, we added 5 ml of a 40% sodium hydroxide solution in water. Overnight, with constant stirring at 40 degrees Celsius, a precipitate formed in the reaction mixture. The aqueous HCl solution was then used to neutralize the reaction mixture. TLC was used to analyse response outcomes. The product was produced after the precipitate was washed with ethanol and then dried in air. The TLC method was used to check the compound's purity. Table 1.1 provides a physicochemical summary of triazole chalcone derivatives.

Table 1.1: Physical and chemical properties of triazole chalcone derivatives (1g-1j)

S. no.	Formula	Mol. Weight	State	Colour	m.p. in °C	Yield %
(1g)	$C_9H_8N_4O$	188	Solid	Turmeric yellow	210 Dec.	75
(1h)	$C_9H_8N_4O$	188	Solid	Turmeric yellow	200Dec.	81
(1i)	$C_{14}H_{16}N_4O_3$	288	Solid	Light yellow	230Dec.	83
(1j)	$C_{14}H_{16}N_4O_3$	288	Solid	Lemon yellow	240Dec.	79

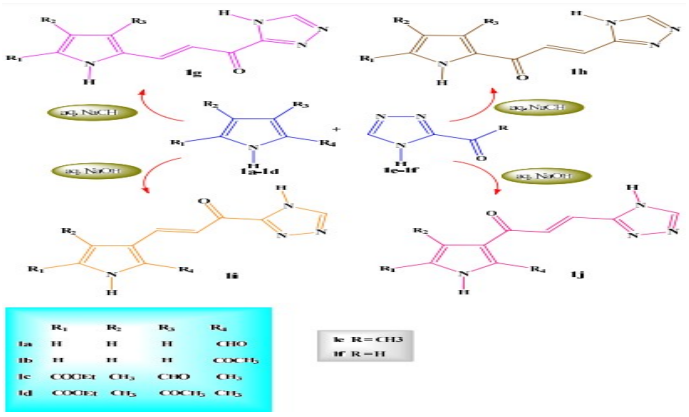


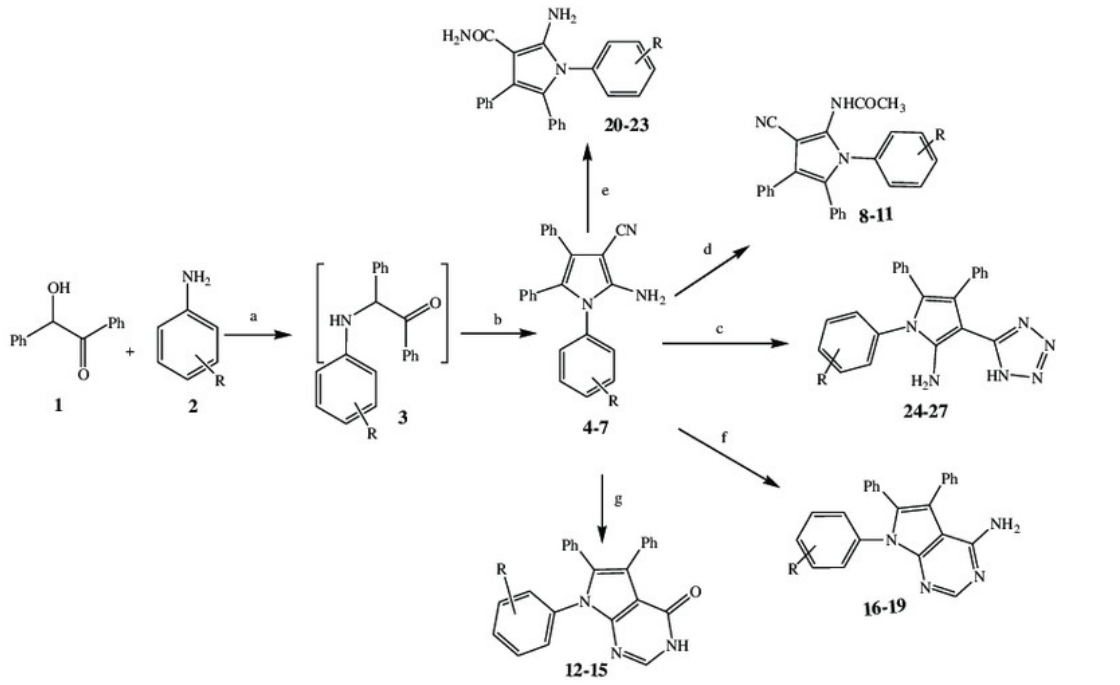
Fig1.4: Synthetic route of 1, 2, 4-triazole-chalcone derivatives.

SYNTHESIS OF TRIAZOLE ISOXAZOLINE DEVIATES AS AN OVERALL PROCEDURE

they produced chemicals and their physical properties in Fig 1.5 and Table 1.2 detail. Two to four drops of HCl were used to catalyse the reaction of 0.0003 mole (100mg) of (1g) / (1h) / (1i) / (1j) in 20ml of ethanol. The reaction mixture was then refluxed at 100°C for 48 hours while being continuously stirred with a solution of 0.001 mole (20mg) hydroxylamine hydrochloride and 5 ml ethanol. The reaction mixture is cooled to room temperature before being poured into ice cold water. The nighttime dew washed and air-dried after collecting on the ground. The substance exhibited a creamy white hue after re-crystallization in methanol. The TLC method is used to check the compound's purity.

Table 1.2: The Physico-chemical characterization of triazoleisooxazoline derivatives (1k–1n)

S. no.	Formula	Mol. Weight	State	Colour	m.p. in °C	Yield %
(1k)	$C_9H_9N_4O$	189	Solid	Creamy white	196-197	80
(1l)	$C_9H_9N_4O$	189	Solid	Light yellow	200	88
(1m)	$C_{14}H_{17}N_5O_3$	303	Solid	Creamy	210	62
(1n)	$C_{14}H_{17}N_5O_3$	303	Solid	Off white	220	68



a = Toluene/HCl/Reflux, b = NC-CH2-CN, c = NaN_3/Reflux, d = Ac_2O/Reflux, e = H^+/NH_3, f = $HCONH_2$/Reflux, g = HCOOH/Reflux. **4,8,12,16,20,24**:R = H; **5,9,13,17,21,25**:R = 2-CH_3; **6,10,14,18,22,26**:R = 3-CH_3; **7,11,15,19,23,27**:R = 4-OCH_3.

Fig1.5: Synthetic route of isooxazoline-triazole derivatives

Conclusion

The target compounds were successfully obtained and described after the experiment. According to the findings of their screening, the antibacterial and antifungal activity rises after chelation or coordination has been performed. Chelation decreases the polarity of the metal ion, which ultimately results in an increase in the metal's lipophilic properties. This lipophilic quality that the metal ions encounter further boosts the effective penetration through the lipid layer of the cell membrane of the microbe, resulting in a more efficient death of the bacteria. In addition, it has been hypothesized that the presence of heteroatoms or certain functional groups in the compounds, such as azomethine (HC=N), may play a significant part in the enhancement of the biological activity of the compounds that have been produced.

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