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SYNTHESIS AND CHARACTERIZATION OF NOVEL HETEROCYCLIC MOLECULES

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Abstract:

The efficient synthesis of novel thiazole and triazole derivatives (3a-3e) has been established by the reaction of p-hydroxy benzoic acid and thiosemicarbazide in the presence of sulphuric acid and sodium hydroxide to yield substituted triazole and thiazole derivatives which on treatment with aryl aldehydes and sulphuric acid forms Schiff Bases. Structures of the synthesized compounds had been elucidated on the basis of spectral data.

Keywords: Triazoles, Thiazoles, Schiff bases, Thiosemicabazide

Introduction:

The art of synthetic chemistry has always been a significant tool in the design of pharmacoactive compounds. A wide screening and development of active analogs is a valuable and widely employed method for drug discovery. Heterocyclic nucleus imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents[1]. Five membered heteroatom containing heterocycles have turned out to be potential chemotherapeutic and pharmacotherapeutic agents. The synthesis of high nitrogen containing heterocyclic compounds has been increasing interest over the past decade because of their utility in various applications. The synthesis of triazole and thiazole fused heterocyclic derivatives has attracted widespread attention due to their diverse biological and pharmacological activities; Mostly researchers have maintained their interest in sulfur and nitrogen-containing heterocyclic compounds through decades of historical development of organic synthesis[2] but heterocycles with other heteroatoms such as oxygen[3], phosphorus[4] and selenium5 also appears. There are widespread therapeutic uses of synthetic heterocycles such as antibacterial, antimycobacterial, trypanocidal, anti-HIV activity, genotoxic, herbicidal, analgesic, antiinflammatory, muscle relaxants, antileishmania agents, anticonvulsant, anticancer, antimalarial, antifungal and lipid peroxidation inhibitor, antitubercular, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents[6-10]. Thiazole was first described by Hantzsch and Waber in 1887. Popp confirmed its structure in 1889[11]. Thiazole's are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug)[12]. In recent times, the applications of thiazoles were found in drug development for the treatment of allergies[13], hypertension[14], inflammation[15], schizophrenia[16], bacterial[17], HIV infections[18], hypnotics[19] and more recently for the treatment of pain, as fibrinogen receptor[20] antagonists with antithrombotic activity[21] and as new inhibitors of bacterial DNA gyrase B[22].

Materials & Methods:

2.1 Materials

Melting points were determined by the open capillary tube method and are uncorrected. FTIR spectra recorded on Perkin Elmer RX1 spectrophotometer using KBr pellets and are expressed in cm−1.The 1H NMR spectra were recorded on Brucker 200 MHz spectrometer in ($CDCl_3$) using TMS as an internal reference

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and chemical shifts is measured in δ ppm. The progress of the reaction was monitored by TLC using 0.2 mm thickness aluminium sheet precoated with Merck Silica gel 60 F254 and visualization was done using iodine/UV lamp or cerric sulfate solution for detection of the spots. All reagents for the chemical synthesis were commercially procured from Sigma Aldrich. All other organic solvents used were of LR grade, dried over anhydrous sodium sulfate and used as received.

2.2 Methods:

2.2.1 Synthesis of p-hydoxy benzoyl thiosemicarbazide (1)

A mixture of p-hydroxy benzoic acid (2.0g, 0.01 mole) and thiosemicarbazide (0.9g, 0.01 mole) in absolute ethanol (20ml) was refluxed for 1-2 hrs. After completion of the reaction, the reaction mixture was monitored by TLC, and then the whole mixture was poured in a beaker containing crushed ice. The solid was separated by filtration, dried over anhydrous sodium sulfate and recrystallised from ethanol to afford the compound 2. The whole process is shown in scheme 1.

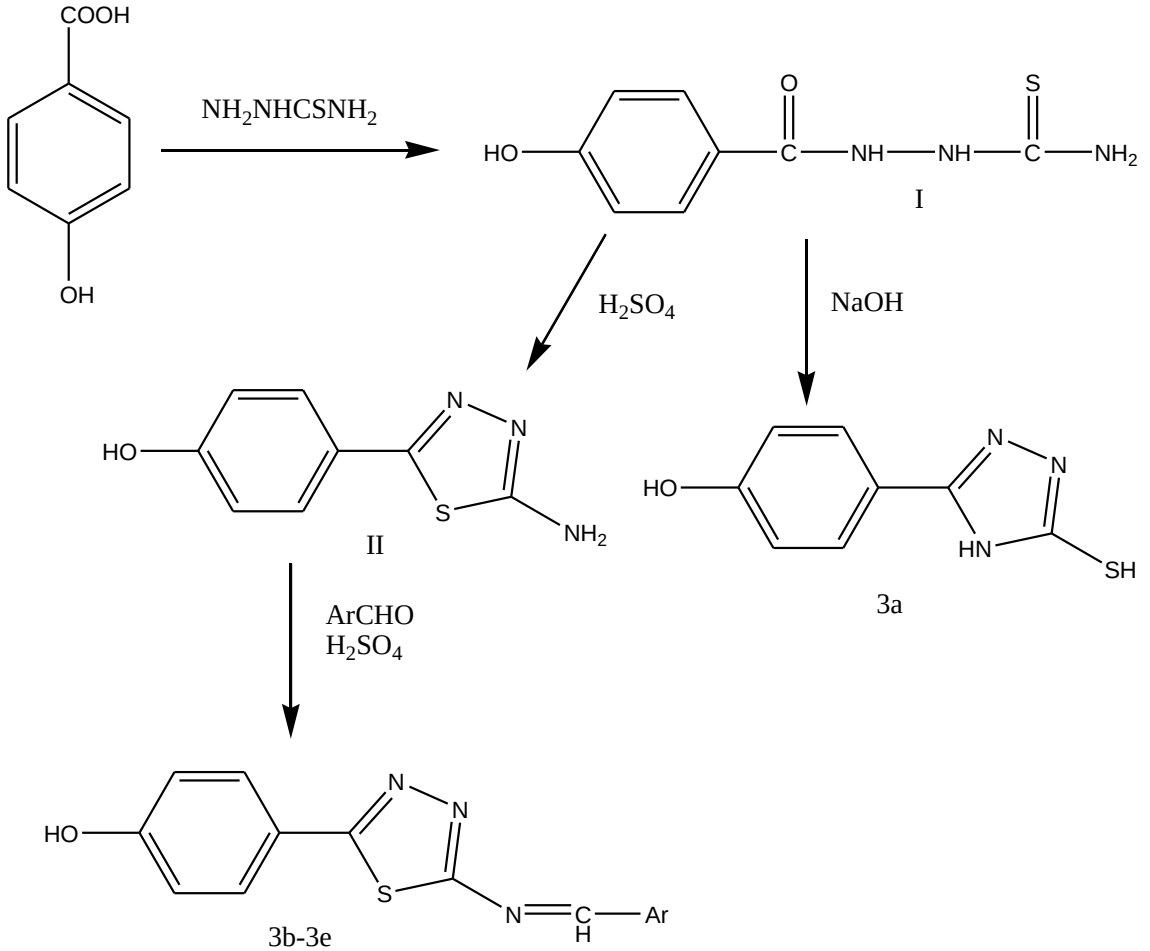
2.2.2. Synthesis of 4-(5-amino-1,3,4-thiadiazol-2-yl)Phenol (2) :

A mixture of compound 1 (1.93 g, 0.01 mole) and a few drops of conc. Sulphuric acid was refluxed for 1.5 hour and poured onto crushed ice. The solid separated out was filtered, washed with cold water and recrystallized from ethanol to separate the product.

2.2.3. Synthesis of 4-(5-mercapto-4H-1,2,4-triazol-3-yl) phenol (3a) : A solution of p-hydoxy benzoyl thiosemicarbazide (1) in 8% NaOH was heated under reflux temperature for 2-3 hrs. The reaction mixture was monitored by TLC and cooled to room temperature and acidified with dilute acetic acid. The solid was separated by filtration, dried over anhydrous sodium sulfate and recrystallized from ethanol to afford the compound.

2.2.4. General procedure for synthesis of 4-(5-substituted amino-1,3,4-thiadiazol-2-yl)Phenol (3b to 3e)

A mixture of compound (2), aryl aldehydes and a few drops of concentrated sulphuric acid in ethanol was refluxed for 5-6 hrs and cooled. After cooling solid was separated by filteration, wash thoroughly with water and recrystallized with ethanol and water (1:1).



WHERE Ar = C_6H_4OH, C_6H_5, $C_6H_4(OCH_3)_2$,$C_6H_4(OH)OCH_3$

Scheme 1: Synthesis of heterocyclic molecules as triazole and thiazole derivatives

Results:

2: 4-(5-amino-1,3,4-thiadiazol-2-yl)phenol:MP 239°C, Yield 54%, IR (KBr): 3425-3756 (NH), 698 (C-S-C), 2931 (C-H, aryl) 2366-2719 (C-H), 1018-1597 (C-N) cm^{-1} ; ^{1}HNMR (DMSO d_6):δ 2.34 (s, 2H, NH_2), 7.4-7.79 (d, 2H, Aryl-CH). 6.87(d, 1H, C-H, Aryl), 7.39(d, 1H, C-H, Aryl), 4.9(s, H, O-H).

3a: 4-(5-mercapto-4H-1,2,4-triazol-3-yl) phenol: MP 310°C, Yield 57%, 3232 (NH), 98 6(C-S-C), 2930 (C-H, aryl) 2360- 63(C-H), 1119 (C-N) cm^{-1} ^{1}H NMR (DMSO d_6): δ 2.99 (s,1H, SH), 7. 31 (d, 2H, Aryl-CH). 6.80(d,1H, C-H, Aryl), 7.31(d,1H, C-H, Aryl), 5(s,1H, O-H).

3b: 4-(5-(benzylideneamino-1,3,4-thiadiazol-2-yl)Phenol : MP 229^0, Yield 50%; IR(KBr): 3452 (NH), 2944 (C-H, Ar), 149 (C=C+C=N), 615 (C-S-C) cm^{-1}. ^{1}HNMR (DMSO $d_{6)}$: δ 6.78(d,2H,C-H, Aryl), 7.42(d, 1H, C-H,Aryl), 6.8(d,1H,C-H,Aryl), 8.12(s, 1H, N=C-H), 7.7(d, 1H, C-H,Aryl), 4.45(s, 1H, O-H, Aryl).

3c: 4-(5-(2-hydroxy-benzylidene)-amino-1,3,4-thiadiazol-2-yl)Phenol : MP 220^0, Yield 50%; IR(KBr): 3452 (NH), 2944 (C-H, Ar), 149 (C=C+C=N), 615 (C-S-C) cm^{-1}. ^{1}HNMR (DMSO $d_{6)}$: δ 6.87(d,2H,C-H, Aryl), 6.77(d,1H C-H,Aryl), 6.70(d,1H,C-H,Aryl),4.41(s,1H,O-H,Aryl) 8.49(s,1H N=C-H), 7.7(s,1H, C-H,Aryl), 4.45(s, 1H, O-H, Aryl).

3d: 4-(5-(3,4-dimethoxy -benzylideneamino-1,3,4-thiadiazol-2-yl) Phenol : MP 225^0, yield 55%; IR(KBr): 3450(NH), 2942 (C-H, Aryl), 1590(C=C and C=N), 625 (C-S-C)cm^{-1}. ^{1}HNMR (DMSO d_6): δ 3.75(s,3H, O-CH_3), 3.63(s, 3H,O-CH_3), 5.54(s, 1H,O-H,Aryl), 6.91(d,1H, C-H, Aryl), 6.98(d,1H C-H, Aryl), 7.01(d,1H, C-H, Aryl), 7.35(d,1H, C-H, Aryl) 8.3(s, 1H, N =C-H), 7.45(s,1H, C-H,Aryl).

3e: 4-(5-(3-dimethoxy-4-hydroxy-benzylideneamino-1,3,4-thiadiazol-2-yl)Phenol: MP 240^0, yield 60%; IR(KBr): 3246(NH), 2942 (C-H, Aryl), 1595(C=C and C=N), 623 (C-S-C)cm^{-1}. ^{1}HNMR (DMSO d_6): δ 3.79(s,3H, O-CH_3), 5.54(s,1H,O-H,Aryl), 6.90(d,1H, C-H, Aryl) 6.98(d,.1H C-H, Aryl), 7.01(d,2H, C-H, Aryl).

Discussion:

In the present work, thiazole and triazole derivatives were prepared using the systematic scheme 1 but the activity profile of the same by further modification in the molecules as complexes with copper were remaining to be optimized. It is required due to high potential of azole derivatives as anti-fouling, anti-bacterial and many other pharmacological activities. So, now a days, many countries focusing on research in development of novel molecules. Also, azole coordination chemistry shows great potential with respect to antifouling coatings for a number of reasons. However, the most promising antifouling approach lies in the very strong affinity of azoles for Cu^{2+} which is a potent antifouling biocide. Thus there is a need to develop the complexes of the azoles with high potential.

Conclusion:

Triazole and thiazole are unique moieties that are responsible for various biological activities. More investigations must be carried out to evaluate the activities of these five membered nitrogen containing moieties for many diseases whose treatment are difficult in the medical sciences. The bioisosteric replacement between the triazole moiety and its bioisostere triazole is responsible for the efficient use of these compounds for the discovery and development of novel triazole drugs. This work focuses to explore more and more synthetic strategies to be develop to synthesize compounds with varied biological applications. This has been noticed so far in the literature, that modifications results in the formation of compounds with valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. Thus many more modifications can be possible and needs to be continued for the use of mankind.

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