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SYNTHESIS AND ANTI-BACTERIAL ACTIVITY OF SOME 1,3,4-THIADIAZOLE AZO COMPOUNDS

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ABSTRACT : Some 1,3,4-thiadiazole azo compounds were prepared by diazotization reaction of Chloro acetamide with different phenols and the product was reacted with 2-amino-5-(4-methoxy phenyl)-1,3,4-thiadiazole to give 2-((substituted phenyl) diazenyl acetamide) amino-5-(4-methoxyphenyl)-1,3,4-thiadiazole (A-F). The compounds were characterized by F.T-IR, ^{1}H-NMR and ^{13}C-NMR. The 1,3,4-thiadiazole azo derivatives (A-F) were tested for their antibacterial activity against (*S. aureus*, *S. epidermidis*, *E. coli* and *P. aeruginosa*) by using disc diffusion method. The minimum inhibitory concentrations (MICs) of the compounds also calculated by agar streak dilution method. The azo-1,3,4-thiadiazole derivatives show moderate activity against the tested bacteria.

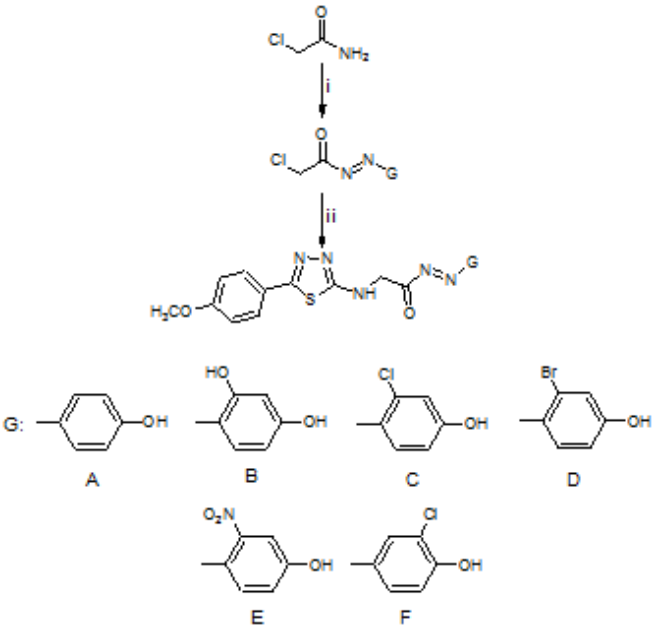
Key words : Azo, amide, 1,3,4-thiadiazole, anti-bacterial.

INTRODUCTION

Azo compounds derivatives are somewhat have essential importance in dyes (Dawson, 1978; Malik and Zadafiya, 2010) and internationally contribute to more than 50% of dyes due to their ease of synthesis and low cost of manufacturing. Azo compounds have different colors starts from yellow to blue-green changing by the substituent (electron withdrawing or releasing group) in the compound. They have significant important in drugs and cosmetics industries (Marmion, 1999) and have a variety of important biological activities and can serve as antibacterial (Awad *et al*, 1998; Makhsumov *et al*, 1991; Ibramin *et al*, 1991; Jarahpour *et al*, 2004), pesticidal (Samadhiya and Halve, 2001), antimicrobial (Eid *et al*, 2004; Goksu *et al*, 2005), anti-HIV-1 anti-inflammatory (Huang *et al*, 2003), activities some azo compounds can serve in the inhibition of protein tyrosine kinases (Burke *et al*, 1993) and inactivation of enveloped viruses. Some azo compounds have liquid crystalline properties (Al-Hamdani *et al*, 2010). This work reports the synthesis and antibacterial activity of some azo -1,3,4-thiadiazole compounds (A-F).

Experimental

The synthesis of the target molecules (A-F) shown in the sequences of reactions depicted in the scheme below. The F.T.IR spectral data recorded on F.T.IR-8400 Fourier Transform Infrared Spectrophotometer SHIMADZU using potassium bromide disc. ^{1}H-NMR and ^{13}C-NMR was recorder on Bruker Ultra Shield, 400MHz, using DMSO as solvent and TMS as internal standard. Melting points (^{o}C) recorded on hot stage Gallen Kamp melting point apparatus and were uncorrected. Some chemicals were purchased from Sigma-Aldrich. Chemical names follow the IUPAC nomenclature.



i) HCl, $NaNO_2$, substituted phenol

ii) 2-amino-5-(4-methoxyphenyl)-1,3,4-thiadiazole, DMF, triethyl amine, reflux (5 hrs).

Synthesis of (substituted phenyl) diazenyl acetamide A1-F1

(Solution 1) chloro acetamide (0.01 mol) was dissolved in 15 mL of 5 M HCl with stirring. The mixture was then cooled to 0°C in an ice bath, then 15 mL of 1 M sodium nitrite solution was added with stirring and the temperature kept below 0°C. (Solution 2) substituted phenols (0.01 mol) in 15 mL of 1 M NaOH at 0°C. (Solution 1) was added slowly with stirring to (solution 2). After 30 min with temperature at 0°C the precipitate was neutralized, filtered and washed with water several times (Vogel, 1989). The physical properties and characteristic IR stretching vibrations for compounds (A1-F1) are shown in Table 1.

Synthesis of 2-((substituted phenyl) diazenyl acetamide) amino-5-(4-methoxy phenyl)-1,3,4-thiadiazole (A-F)

A mixture of (A1-F1) (0.01 mol) and 2-amino-5-(4-methoxyphenyl)-1,3,4-thiadiazole (0.01 mol) was dissolved in 50 mL DMF; triethyl amine 0.015 mol was added. The mixture refluxed for 5 hrs, water then added and the precipitate was filtered and washed with water (Shneshil, 2017).

(A) yield 80 %, m.p 246 °C, F.T-IR (KBr) cm^{-1}, 3450 cm^{-1}, 3397 cm^{-1}, 3094cm^{-1}, 2965-2855 cm^{-1}, 1676 cm^{-1}, 1623 cm^{-1}, 1610 cm^{-1}, 1594 cm^{-1}, ^{1}H-NMR (DMSO) ä: 7.2-8.1 (m,7H), 6.1 (s,1H), 5.4 (s,1H), 4.7 (S,2H), 3.9 (s,3H), ^{13}C-NMR (DMSO) ä: 33,41,124-145,156,176.

(B) yield 82 %, m.p 264 °C, F.T-IR (KBr) cm^{-1}, 3455 cm^{-1}, 3276 cm^{-1}, 3091 cm^{-1}, 2962-2843 cm^{-1}, 1671 cm^{-1}, 1620 cm^{-1}, 1605 cm^{-1}, 1590 cm^{-1}, ^{1}H-NMR (DMSO) ä: 7.2-8.2 (m,7H), 5.9 (s,2H), 5.2 (s,1H), 4.4 (S,2H), 3.6 (s,3H), ^{13}C-NMR (DMSO) ä: 31,48,122-144,151,169.

(C) yield 76 %, m.p 254 °C, F.T-IR (KBr) cm^{-1}, 3456 cm^{-1}, 3255 cm^{-1}, 3105 cm^{-1}, 2947-2861 cm^{-1}, 1665 cm^{-1}, 1629 cm^{-1}, 1615 cm^{-1}, 1598 cm^{-1}, ^{1}H-NMR (DMSO) ä: 7.1-8.4 (m,7H), 6.5 (s,1H), 5.3 (s,1H), 4.4 (S,2H), 3.6 (s,3H), ^{13}C-NMR (DMSO) ä: 29,45,119-140,152,165.

(D) yield 84 %, m.p 255 °C, F.T-IR (KBr) cm^{-1}, 3452 cm^{-1}, 3243 cm^{-1}, 3101 cm^{-1}, 2954-2833 cm^{-1}, 1653 cm^{-1}, 1624 cm^{-1}, 1609 cm^{-1}, 1591 cm^{-1}, ^{1}H-NMR (DMSO) ä: 7.6-8.8 (m,7H), 6.6 (s,1H), 5.1 (s,1H), 4.7 (S,2H), 3.8 (s,3H), ^{13}C-NMR (DMSO) ä: 33,52,123-149,158,175.

(E) yield 73%, m.p 234°C, F.T-IR (KBr) cm^{-1}, 3477 cm^{-1}, 3231 cm^{-1}, 3103 cm^{-1}, 2976-2865 cm^{-1}, 1686 cm^{-1}, 1633 cm^{-1}, 1615 cm^{-1}, 1593 cm^{-1}, ^{1}H-NMR (DMSO) ä: 7.3-8.6 (m,7H), 6.3 (s,1H), 5.5 (s,1H), 4.9 (S,2H), 4.1 (s,3H), ^{13}C-NMR (DMSO) ä: 37,49,119-153,162,174.

(F) yield 77%, m.p 242°C, F.T-IR (KBr) cm^{-1}, 3461cm^{-1}, 3252 cm^{-1}, 3092cm^{-1}, 2955-2842 cm^{-1}, 1654 cm^{-1}, 1619 cm^{-1}, 1598 cm^{-1}, 1583 cm^{-1}, ^{1}H-NMR (DMSO) ä: 7.5-8.3 (m,7H), 6.2 (s,1H), 5.8 (s,1H), 4.3 (S,2H), 3.7 (s,3H), ^{13}C-NMR (DMSO) ä: 31, 52, 121-149, 148, 171.

Antibacterial activity

The antibacterial activity of the compounds (A-F) was investigated against two Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) using nutrient agar medium. The sterilized (autoclaved at 120°C for 30 min) medium (40-50°C) was inoculated (1 mL/100 mL of medium) with the suspension (105 cfu mL^{-1}) of the microorganism (matched to McFarland barium sulfate standard) and poured into a petridish to give a depth of 3-4 mm (Gillespie, 1994). The paper was impregnated with the tested compounds (µg mL^{-1} in DMF) and placed on the solidified medium. The plates were incubated at 37°C for 24. The inhibition zones are shown in Table 2. MIC for the synthesized compounds was calculated by agar streak dilution method (Panneerselvam *et al*, 2009). A stock solution of the compound (100 µg mL^{-1}) in DMF was prepared and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar (nutrient agar). A specified quantity of the medium (40-50°C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. Suspension of the microorganism was prepared to contain approximately 105 cfu mL^{-1} and applied to plates with serially diluted compounds in DMF to be tested and incubated at 37°C for 24 hrs. The MIC represents the lowest concentration of the tested substance showing no visible growth of bacteria on the plate. The MIC is shown in Table 2.

RESULTS AND DISCUSSION

The synthesis involves the diazotization reaction of chloro acetamide with phenol (A1) and five substituted phenols resorcinol (B1), *m*-chloro phenol (C1), *m*-bromo phenol (D1), *m*-nitro phenol (E1) and *o*-chloro phenol (F1)). Azo compounds A1-F1 then reacted with 2-amino-5-(4-methoxyphenyl)-1,3,4-thiadiazole to give compounds (A-F). The compounds (A-F) were purified by multiple recrystallization from ethyl acetate, ethanol and characterized by using F.T.IR, ^{1}H-NMR and ^{13}C-NMR. The anti-bacterial activity was tested using disc diffusion method. There is no misgiving that antimicrobial agents play major role to save the human race from infectious disease which causing by pathogenic bacteria. Without antimicrobial agents, millions of people will become

Table 1 : physical properties and characteristic IR stretching vibrations (ί cm^{-1}) for compounds (A1-F1).

Comp. no.	% yield	M.P. (°C)	O-H	C-H aromatic	C-H Aliphatic	C = O	N = N
A1	77	215	3452	3090	2960-2854	1675	1594
B1	80	245	3447	3098	2966-2848	1668	1597
C1	75	221	3453	3108	2952-2855	1663	1592
D1	69	235	2458	3109	2950-2841	1653	1590
E1	83	205	3477	3103	2974-2861	1685	1593
F1	71	229	3462	3092	2952-2844	1653	1582

Table 2 : Antibacterial activity and (MIC) for the synthesized compounds (A-F).

Compound No.	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*
A	9(14)	8(16)	11(12)	6(15)
B	7(11)	9(13)	13(17)	8(12)
C	9(11)	12(15)	11(16)	8(14)
D	10(21)	13(17)	15(16)	9(11)
E	12(11)	13(14)	11(13)	7(18)
F	11(12)	9(11)	8(17)	13(14)

victims to infectious diseases. Pathogenic bacteria are a major target for antimicrobial agents; therefore, many of them have evolved mechanisms to resist these agents. These resistance mechanisms can be contribute to their ability to survive within the host, as well as increase their virulence. Presently, antibacterial resistance is become a serious threat to infectious disease management globally. Generally there are several different mechanisms for these agents action, includes inhibition of cell wall synthesis, of ribosome function, of nucleic acid synthesis, of folate metabolism or of cell membrane function. The resistance mechanisms therefore depend on which pathways the drugs inhibit and whether the organisms can modify those pathways (Yeaman and Yount, 2003). The minimum inhibitory concentrations (MICs) of the compounds measured using agar streak dilution method. The results show that the compounds have moderate activity against the used microbes.

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