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Synthesis and Biological Evaluation of Thiazolidinone Derivatives as Antimicrobial Agents

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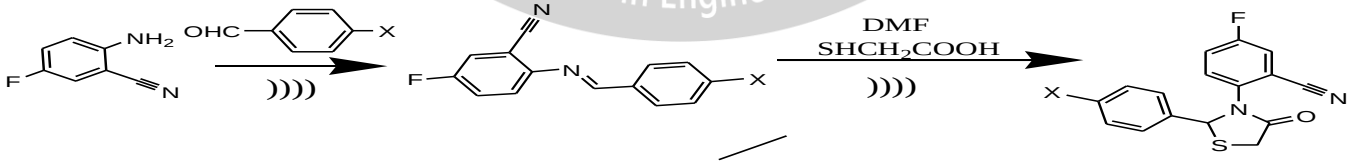
Abstract - New series of 5-fluoro-2-(2-(4-substitutedphenyl)-4-oxothiazolidin-3-yl)benzonitrile, 3(a-e) have been synthesized from Schiff bases 2(a-e). Schiff bases were synthesized by condensation of 2-amino-5-fluorobenzonitrile with substituted aromatic aldehyde by conventional as well as sonication method thus providing unique chemical processes with special attributes such as enhanced reaction rates and higher yields. All the synthesized compounds were screened for their antibacterial and antifungal activities against some gram positive and gram negative stains. The structure of the synthesized compounds was confirmed by chemical and spectral analysis like IR, ^{1}H NMR and ^{13}C NMR.

Keywords: 2-amino-5-fluorobenzonitrile, Thiazolidinone, Conventional, Antimicrobial and antifungal.

I. INTRODUCTION

4-thiazolidinone nucleus has occupied a unique place in the field of potential pharmaceutical applications. The reactions begin by formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by generated sulfur nucleophile, followed by intramolecular cyclization on elimination of water.[1],[2],[3], As of late, this system containing compounds were successful against antimicrobial. Thiazoles are heterocyclic compound containing nitrogen and sulfur particles in their structure and are turned out to be clinically valuable specialists against various types of diseases. Thiazole derivatives have been employed in the preparation of different important drugs required for treatment of Antibacterial [4], Antifungal [5], Antitubercular [6], Anticancer [7], Antiinflammtory [8], Analgesic [9], Anticonvulsant [10], Antidepressant [11], Antiviral [12], Anti-HIV [13], Antidiabetic [14] and Antiarrhythmic [15].



1 2a-e 3a-e

Scheme 1

(X= H, Cl, F, -CH_3, -OCH_3)

II. MATERIALS AND METHODS

2.1 Experimental

Melting points were taken in open capillaries are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates using MeOH: $CHCl_3$ system (2:8). The spot was visualized by exposing dry plate at iodine vapours chamber. IR spectra were recorded in KBr disc on Schimadzu 8201 PC, FTIR spectrophotometer (Vmax in cm-1) and ^{1}H NMR and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 and 75 MHz using TMS as an internal standard respectively. All chemical shifts were reported on δ scales. The analytical data of all the compounds were highly satisfactory. For column chromatographic purification of the products Merck silica Gel 60 (230-400 Mesh) was used. The analar grade chemicals were purchased from the commercial sources and further purified before use.

2.2. General Sonication method for synthesis of compound 2(a-e) and 3(a–e)

2.2.1 General procedure for the synthesis of Schiff bases 2(a-e)

2-amino-5-fluorobenzonitrile (1) (1mmol), Substituted aromatic aldehydes (1mmol) and 95% ethanol (20 ml) were taken into a 100 ml conical flask. Sample was exposed to intense ultrasonic irradiation the amplitude of the ultrasonic device UP400 S (400W, 24 kHz) was set to 50 % sonication was applied for 90 min at room temperature. The sonotrode of the ultrasonic liquid processors UP4000 S was immersed directly into the reaction solution. The completion of the reaction was monitored by silica gel-G coated TLC plates. After the completion of the reaction the product was filtered with suction on a Buchner funnel. The

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purified product was dried under vacuum and recrystallized from ethanol at room temperature to yield compound **2a-e**.

2.2.2 (E)-2-(benzylideneamino)-5-fluorobenzonitrile (2a) Yield: 82%; m.p. 90°C. M.F; C_{14} H_9FN_2; IR (KBr pellet,) *v*max cm^{-1}: 1510 (C=C str), 3060 (Ar C-H str), 1587 (HC=N), 2937 (C-H str) ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.60 (S, 1H, HC=N), 6.87 - 7.38 (m, 8H, Ar-H); ^{13}C NMR (DMSOd6) (δ/ppm): 118.44-133.58 (Ar-C), 163.97 (C=N). Anal. Calcd. For: C_{14} H_9FN_2: C, 74.99; H, 4.05; N, 12.49. Found: C, 74.97; H, 4.02; N, 12.47.

2.2.3 (E)-2-(4-chlorobenzylideneamino)-5-fluorobenzonitrile (2b) Yield: 85%; m.p. 116 °C. M.F; $C_{14}H_8ClFN_2$; IR (KBr pellet,) *v*max cm^{-1}: 1508 cm^{-1} (C=C str) 3053 cm^{-1}(Ar C-H str), 1591 cm^{-1}(HC=N), 2931 cm^{-1} (C-H str) ;^{1}H NMR ($CDCl_3$) (δ/ppm): 9.87 (S, 1H, HC=N), 7.03-8.04 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$) (δ/ppm): 118.53-134.60 (Ar-C), 165.01 (C=N). Anal. Calcd. For: $C_{14}H_8ClFN_2$: C, 65.00; H, 3.12; N, 10.83. Found: C, 65.01; H, 3.13; N, 1.82.

2.2.4 (E)-2-(4-fluorobenzylideneamino)-5-fluorobenzonitrile (2c) Yield: 85%; m.p. 122°C. M.F; $C_{14}H_8F_2N_2$; IR (KBr pellet,) *v*max cm^{-1}: 1506 cm^{-1} (C=C str) 3062 cm^{-1}(Ar C-H str), 1589 cm^{-1}(HC=N), 2931 cm^{-1} (C-H str) ;^{1}H NMR ($CDCl_3$) (δ/ppm): 8.50 (S, 1H, HC=N), 7.07-8.48 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$) (δ/ppm): 115.09-131.98 (Ar-C), 149.66 (C=N) . Anal. Calcd. For: $C_{14}H_8F_2N_2$: C, 69.42; H, 3.33; N, 11.57. Found: C, 69.41; H, 3.33; N, 11.60.

2.2.5 (E)-5-fluoro-2-((4-methylbenzylidene) amino)benzonitrile (2d) Yield: 82%; m.p. 85 °C. M.F; C_{15} H_{11} FN_2; IR (KBr pellet,) *v*max cm^{-1}: 1539 cm^{-1} (C=C str) 3030 cm^{-1}(Ar C-H str), 1562 cm^{-1}(HC=N), 2908 cm^{-1} (C-H str) ; ^{1}H NMR ($CDCl_3$) (δ/ppm): 8.17 (S, 1H, HC=N), 2.50 (S,3H,-CH_3), 6.35-7.81 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$) (δ/ppm): 116.62-134.60 (Ar-C), 160.36 (C=N), 29.68(-CH_3). Anal. Calcd. For: $C_{15}H_{11}FN_2$: C, 75.62; H, 4.65; N, 11.76. Found: C, 75.61; H, 4.64; N, 11.72.

2.2.6 (E)-2-(4-methoxybenzylideneamino)-5-fluorobenzonitrile (2e) Yield: 83%; m.p. 107 °C. M.F; $C_{15}H_{11}FN_2O$; IR (KBr pellet,) *v*max cm^{-1}: 1508 cm^{-1} (C=C str) 3062 cm^{-1}(Ar C-H str), 1598 cm^{-1}(HC=N), 2927 cm^{-1} (C-H str) ; ^{1}H NMR ($CDCl_3$) (δ/ppm): 9.40 (S, 1H, HC=N), 6.33-7.80 (m, 7H, Ar-H), 3.39 (S,3H,(-OCH_3); ^{13}C NMR ($CDCl_3$) (δ/ppm): 127.92-139.93 (Ar-C), 145.43 (C=N), 56.49 (-OCH_3). Anal. Calcd. For: C_{15} H_{11} FN_2O: C, 70.86; H, 4.36; N, 11.02. Found: C, 70.84; H, 4.32; N, 11.04.

III. General Procedure for the Synthesis of Thiazolidinone

3(a-e)

A mixture of (E)-2-(4-substituted benzylideneamino)-5-fluorobenzonitrile (0.01mol) and thioglycollic acid (0.01mol) were suspended in DMF (60ml). Catalytic amount of zinc chloride (1g) was added to it and exposed to intense ultrasonic irradiation the amplitude of the ultrasonic device UP400 S (400W, 24 kHz) was set to 50 % sonication was applied for 90 min at room temperature. The sonotrode of the ultrasonic liquid processors UP4000 S was immersed directly into the reaction solution. The product obtained was poured over ice water. The solid separated out was filtered, washed with water and recrystallized from ethanol.

3.1.1 5-fluoro-2-(4-oxo-2-phenylthiazolidin-3-yl)benzonitrile (3a) Yield: 68 %; m.p. 245-246°C. Light yellow colour, M.F; $C_{16}H_{11}FN_2OS$; IR (KBr pellet,) *v* max cm^{-1}: 2920 (Ali C-H str.), 3039 (Ar C-H str.),1510 (Ar C=C str.), 1660 (C=O), 692 (C-S-C), 2266 (C-CN),1184 (C-F); ^{1}H NMR (CDCl3) (δ/ppm): 3.20 (S,2H, CH_2), 6.80-7.66 (m, 8H, Ar-H), 3.917 (S,1H,(CH); ^{13}C NMR (CDCl3) (δ/ppm): 170.76 (C=O), 82.97 (C-H), 40.40 (CH_2), 123.4-131.09 (Ar C),113.9 (CN)

3.1.2 2-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-5-fluorobenzonitrile (3b) Yield: 67 %; m.p. 283-284°C. Yellow colour, M.F; $C_{16}H_{10}ClFN_2OS$; IR (KBr pellet,) *v* max cm^{-1}: 2926 (Ali C-H str.), 3035 (Ar C-H str.),1504 (Ar C=C str.), 1653 (C=O), 675 (C-S-C), 2202 (C-CN), 1166 (C-F); ^{1}H NMR (CDCl3) (δ/ppm): 3.26 (S,1H, CH-Cl), 6.77-8.04 (m, 7H, Ar-H), 5.15 (S,1H,(CH_2); ^{13}C NMR (CDCl3) (δ/ppm): 161.02 (C=O), 79.20 (C-H), 43.74(CH_2), 120.32-136.9 (Ar C),120.32 (CN)

3.1.3 5-fluoro-2-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl) benzonitrile (3c) Yield: 68 %; m.p. 291-292°C. Yellow colour, M.F; $C_{16}H_{10}F_2N_2OS$; IR (KBr pellet,) *v* max cm^{-1}: 2920 (Ali C-H str.), 3030 (Ar C-H str.),1500 (Ar C=C str.), 1654 (C=O), 677 (C-S-C), 2357 (C-CN), 1176 (C-F); ^{1}H NMR (CDCl3) (δ/ppm): 3.49 (S,2H, CH_2), 6.69-8.00 (m, 7H, Ar-H), 5.17 (S,1H,(CH); ^{13}C NMR (CDCl3) (δ/ppm): 161.01 (C=O), 43.64 (CH_2), 79.26(CH), 120.96-137.64 (Ar C), 119.41 (CN)

3.1.4 5-fluoro-2-(4-oxo-2-p-tolylthiazolidin-3-yl)benzonitrile (9) Yield: 65 %; m.p. 270-271°C. Pale yellow, M.F; $C_{17}H_{13}FN_2OS$; IR (KBr pellet,) *v* max cm^{-1}: 2920 (Ali C-H str.), 3030 (Ar C-H str.),1508 (Ar C=C str.), 1654 (C=O), 686 (C-S-C), 2358 (C-CN), 1172 (C-F); ^{1}H NMR (CDCl3) (δ/ppm): 2.20 (S,2H, CH_2), 6.83-8.00 (m, 7H, Ar-H), 5.26 (S,1H,(CH), 2.39 (S,3H,(CH_3), ^{13}C NMR (CDCl3) (δ/ppm): 163.06 (C=O), 43.65 (CH_2), 79.96 (CH), 124.29-138.95 (Ar C), 122.56 (CN)

3.1.5 5-fluoro-2-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)benzonitrile (10)) Yield:70 %; m.p. 262-263°C, Yellow Colour, M.F; $C_{17}H_{13}FN_2O_2S$; IR (KBr pellet,) *v* max cm^{-1}: 2918 (Ali C-H str.), 3030 (Ar C-H str.),1512 (Ar C=C str.), 1660 (C=O), 692 (C-S-C), 2357 (C-CN), 1184 (C-F); ^{1}H NMR (CDCl3) (δ/ppm): 3.76(S,2H, CH_2), 6.85-8.05 (m, 7H, Ar-H), 6.74 (S,1H,(CH), 3.89 (S,3H,(OCH_3), ^{13}C NMR (CDCl3) (δ/ppm): 163.59 (C=O),

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36.35 (CH_2), 79.99 (CH), 122.05-135.18 (Ar C), 122.01 (CN).

Table 1.Data of yield and reaction time of all synthesised compounds.				
Compound	Yield %		Reaction Time (min.)	
	Conventional	Sonication	Conventional	Sonication
2a	80	82	1.15	50
2b	82	85	1.20	45
2c	75	85	1.15	45
2d	78	82	1.50	46
2e	75	83	1.20	55
3a	78	88	2.00	70
3b	76	87	2.30	90
3c	68	88	2.45	78
3d	67	85	2.30	80
3e	68	80	2.10	80

Table 2. Antibacterial and antifungal activities of compounds 3(a-e).										
Compound	Zone of inhibition in diameter (mm)									
	BA	SA	EC	SP	PA	AF	AN	FO	PC	TV
3a	7	12	-	19	15	14	14	15	18	-
3b	10	12	8	15	12	-	14	-	-	16
3c	12	-	8	15	12	-	18	24	13	14
3d	12	-	11	-	-	14	22	21	14	-
3e	-	16	6	24	-	18	24	21	15	16
Streptomycine	27	24	26	20	22					
Amphotericin-B						22	25	26	17	22

BA:Bacillus subtilis,SA:Staphylococcus aureus,EC:Escherichia coli,SP:Streptococcus Pyogenes,PA:Pseudomonasaeruginosa,AF:Aspergillusflavus,AN:Aspergillusniger, FO:Fusariumoxysporum,PC:Penicillimchryogenum, TV:Trigoderma viride

IV. RESULTS AND DISCUSSION

The compound 1 gave the condensation reaction with substituted benzaldehydes resulting in the production of Schiff bases N,CH, compound 2(a-e) which was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectra of compound 2(a-e). In the IR spectra an absorption was found in the range of 1589–1598 cm^{-1} while a strong signal appeared in the range of d 8.60–9.40 and d 118.44–139.93 ppm in the ^{1}H NMR and ^{13}C NMR spectra for N,CH of compound 2(a-e) respectively. The facts have also supported by the disappearance of the signal of NH_2 in the ^{1}H NMR spectra. The compound 2(a-e) on reaction with equimolar amount of thioglycolic acid in the presence of $ZnCl_2$ (act as a catalyst) in the trace amount gives the cycloaddition reaction and produced a five membered thiazolidinone ring, compound 3(a–e) The compound 3(a–e) showed a characteristic absorption for the cyclic carbonyl group in the range of 1653-1660 cm^{-1} in the IR spectra. The ^{1}H NMR spectra aroused our attention and clearly indicate the presence of the two active methylene protons in the thiazolidine ring in the range of d 3.15–3.76 ppm. The ^{13}C NMR spectra of compound 3(a-e) also supported the fact that cyclic carbonyl group present and a signal appeared in the range of d 161.02-170.75 ppm.

These all above facts clearly confirmed the synthesis of all final products. All above compounds 2(a-e) and 3(a–e) were also synthesized by sonication method. Characterization data were given in Table 1. All these above facts clearly confirmed the synthesis of all final products.

Antimicrobial data (as shown in Tables 2) revealed that all the synthesized compound 3(a-e) have a structure activity relationship (SAR) because activity of compounds varies with substitution. Electron donating group increases the rate of the reaction so reactivity of the compound (3c, 3d and 3e) showed higher activity than chloro (3b) compound. On the basis of SAR, it was concluded that the activity of compounds depends on the electron donating nature of the substituted groups. The sequence of the activity is following Cl < F < CH_3 < OCH_3..

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V. CONCLUSION

Compound 2(a-e) and 3(a-e) were synthesized by conventional and sonication methods, reaction time and yields of the synthesized compound displayed that sonication method is more efficient than the conventional method. Compound 2(a-e) and 3(a-e) were screened for their antibacterial and antifungal activity against selected microorganisms. The investigation of antimicrobial data revealed that the compounds (3c), (3d) and (3e) displayed highly active in the series, compounds (3b) showed moderate activity and rest compounds showed less activity against all the strains compared with standard drugs.

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