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Article

Synthesis of Novel Biologically Active Thiazole dyes and their applications

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Abstract: This work is aiming to motivation on the prospect of evolving new thiazole dyes with respectable application properties, expected pharmacological activities. Curcumin Coupling with diverse diazonium salts of 2-amino thiazole derivatives as 2-aminobenzothiazole, 2-amino-5-phenylthiazole, 2 amino-5-methylthiazole and 2 amino-5-nitrothiazole to produce novel azo dyes. All synthesised dyes were completely confirmed their structures *via* elemental and spectroscopic techniques. The synthesised thiazole derivatives were examined for their "antimicrobial, anticancer and antioxidant" activities. All of the synthesized dyes were applied on synthetic fabrics as polyester and successively their dyeing properties, "light, washing, perspiration, rubbing and sublimation" fastness were evaluated. Prepared dyestuffs are suitable for dyeing polyester fabrics. It was initiate that all of prepared dyes own extraordinary colour hue, along with respectable fastness properties. Also the synthesised thiazole derivatives display moral pharmacology activity.

Keywords: Thiazolyl dyes; Anticancer; Antioxidant; Colour assessment

1. Introduction

The Curcumin is the most popular yellow and red natural dyes, respectively. Curcumin is a vigorous constituent in turmeric "Curcuma longa L" that is utilized as a nutrition pigment [1]. Turmeric is a standout amongst the most prominent restorative herbs, with an extensive variety of pharmacological efficacy, for example, antioxidant [2] anti-protozoal [3], "anti-inflammatory" [4], anti-proliferative [5], anti-tumor and anti-aging properties [6]. Curcuminoids have realized the prospective therapeutic curiosity to cure "immune related, metabolic diseases and cancer" owing to a enormous numeral of biotic objects and effectively no lateral effects [7].

Regardless of critical advances in antiviral drug improvement amid the previous two decades, viral infections keep on causing genuine horribleness and mortality around the world. Diverse antiviral drugs are presently accessible for the treatment of diseases by HIV, herpes-, flu, hepatitis B or hepatitis C infections. Aside from the expansive antiviral specialist ribavirin, there is no endorsed treatment for differing rising RNA viruses. Likewise, new antiviral molecules are required to handle the issues of medication poisonous quality and fast improvement of drug resistance, which is especially dangerous for transformation inclined RNA viruses. Since virus replication happens inside host cells, and host cell digestion and viral replication are firmly integrated, the improvement of compounds which specifically meddle with infection particular process is one of the primary difficulties in antiviral drug design.

Thiazole derivatives can have diverse pharmacological properties, for instance antioxidant [8], cytotoxic [9], anti-infectious [10], antimicrobial [11]. There have been a few reports on thiazole derivatives displaying antiviral activities [12] . Herein this work is aimed to synthesis of novel thiazolyl curcumin derivatives and evaluated their potential antiviral properties in cell-based assays.

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We chose to combine the curcumin skeleton with a thiazolyl ring. Several researchers have incorporated this moiety into various biologically active compounds [13].

2. Materials and Methods

All melting points are uncorrected and have been measured by a Gallenkamp melting point apparatus. FTIR spectrophotometer PyeUnicam SP-3-300 was used *via* potassium bromide disks. ^{1}H-NMR spectra were run at 400 MHz, on a Varian Mercury VX-300 NMR spectrometer using (DMSO-d6) and chemical shifts (ɷ) were mentioned in ppm. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70 eV at the Micro analytical Centre.

2.1. General procedure for 2-(thiazol-2-yl)hydrazono curcumin (3a-d)

Solid sodium nitrite (0.69g) was solubilized slowly in warm conc H_2SO_4 (5.3 mL) and cooled to 0-5°C then added dropwise to cooled solution of different aminothiazole in suphuric acid. Morover, diazonium salt n was added dropwise through stirring to cold solution of curcumin **2** in sodium hydroxide (0.5M) (3.68 g in 20 ml).The reaction was Stirred for 2h at 0-5°C and the reaction was filtered, ppt was washes away by water, dried and re-crystallised from ethanol.

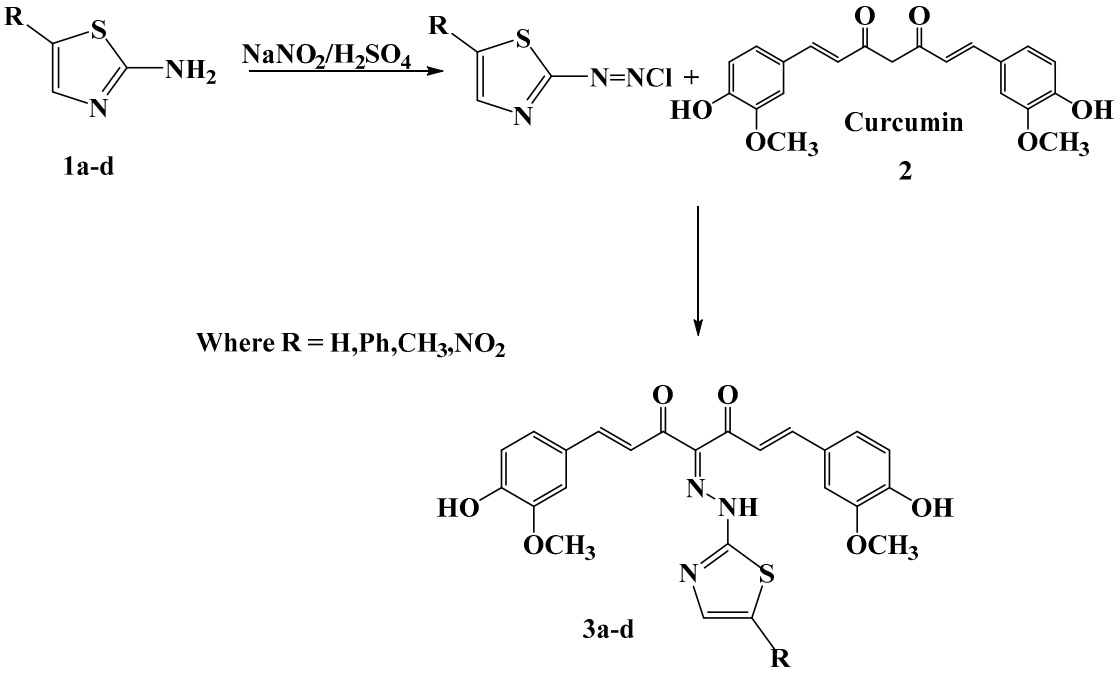

Figure 1. synthesized compounds **3a-d**.

2.2. 1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(2-(thiazol-2 yl)hydrazono)hepta-1,6-diene-3,5-dione (3a)

Red solid, ethanol, yield: 68 per cent, mp – 238-239°C; IR (KBr, νmax/ cm-1): 3410,3502 (2OH), 3312,3318 (2NH), 1691 (C=O), 1660 (C=N), 1551 (C=N), 1510(C=C conjugated); 1HNMR (400 MHz, DMSO-d6, ɷ/ppm): 3.62 (s, 6H, 2OCH3), 5.61(s,2H,2OH),6.49 (s,2H,vinylic H, J=12 Hz),6.91-7.42(m, 8H, ArH), 7.98 (s, 1H, =NNH), ; MS, m/z (%): 479 (M ±, 47), 454 (54.2), 396 (65.7), 368 (100). Anal. Calcd. For C24H21N3O6S (479.51): C60.12; H, 4.41; N, 8.76; S, 6.69 per cent, Found: C, 60.09; H, 4.69; N, 8.72; S 6.64 percent.

2.3. *1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(2-(4-phenylthiazol-2-yl)hydrazono)hepta-1,6-diene-3,5-dione (3b)*

Red solid, ethanol, yield: 68 per cent, mp – 276-278°C; IR (KBr, νmax/ cm-1): 3412,3521 (2OH), 3265,3327 (2NH), 1695 (C=O), 1664 (C=N), 1553 (C=N), 1509(C=C conjugated); 1HNMR (400 MHz, DMSO-d6, ɷ/ppm): 3.68 (s, 6H, 2OCH3), 5.64(s,2H,2OH),6.52 (s,2H,vinylic H, J=12 Hz),6.92-7.64(m, 12H, ArH), 7.79 (s, 1H, =NNH), ; MS, m/z (%): 555 (M ±, 39), 442 (51.6), 381 (68.4), 368 (100). Anal.

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Calcd. For C30H25N3O6S (555.61): C64.85; H, 4.54; N, 7.56; S, 5.77 per cent, Found: C, 64.48; H, 4.47; N, 7. 58; S 5.68 percent.

2.4. 1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(2-(4-methylthiazol-2-yl)hydrazono)hepta-1,6-diene-3,5-dione (3c)

Red solid, ethanol, yield: 64 per cent, mp – 291-292°C; IR (KBr, νmax/ cm-1): 3412,3519 (2OH), 3255,3331 (2NH), 1692 (C=O), 1665 (C=N), 1555 (C=N), 1511(C=C conjugated); 1HNMR (400 MHz, DMSO-d6, ϭ/ppm): 2.57 (s, 3H, CH3), 3.56 (s, 6H, 2OCH3), 5.68(s,2H,2OH),6.41 (s,2H,vinylic H, J=12 Hz),6.92-7.64(m, 8H, ArH), 7.76 (s, 1H, =NNH), ; MS, m/z (%): 455 (M ±, 41.5), 423 (57.3), 396 (68.7), 368 (100). Anal. Calcd. For C25H23N3O6S (493.53): C60.84; H, 4.70; N, 8.51; S, 6.50 per cent, Found: C, 60.78; H, 4.60; N, 8. 39; S 6.39 percent.

2.5. 1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(2-(4-nitrothiazol-2-yl)hydrazono)hepta-1,6-diene-3,5-dione (3d)

Red solid, ethanol, yield: 74 per cent, mp – 251-252°C; IR (KBr, νmax/ cm-1): 3411,3502 (2OH), 3264,3336 (2NH), 1696 (C=O), 1671 (C=N), 1558 (C=N), 1509(C=C conjugated); 1HNMR (400 MHz, DMSO-d6, ϭ/ppm): 3.62 (s, 6H, 2OCH3), 5.65(s,2H,2OH),6.47 (s,2H,vinylic H, J=12 Hz),6.97-7.72(m, 8H, ArH), 7.79 (s, 1H, =NNH), ; MS, m/z (%): 524 (M ±, 39.6), 455 (54.6), 381 (66.4), 368 (100). Anal. Calcd. For C24H20N4O8S (524.50): C54.96; H, 3.84; N, 10.68; S, 6.11 per cent, Found: C, 54.83; H, 3.68; N, 10.57; S 6.01 percent.

2.6. Antimicrobial activity

Antimicrobial activity of the synthesised compounds have been tested against microorganisms via disc–agar diffusion method [14].

2.7. Organisms testing

Agricultures for microorganism were tested according to standard methods for "Staphylococcus aureus (ATCC25923) and Bacillus subtilis (ATCC6635) as gram-positive bacteria, Escherichia coli (ATCC 25,922) and Salmonella typhimurium (ATCC 14,028)" as gram-negative bacteria, Chloramphenicol was used as standard drug:, Yeast: "Candida albicans (ATCC 10,231) and Fungus: Aspergillus fumigatus".

2.8. Antimicrobial prospective

Antibacterial efficacies for the synthesised compounds were dispensed rendering to inhibition zones method through Mueller–Hinton agar plates. Inoculated disc were tested by millimetre ruler, after incubation, the diameters of inhibition zones were measured and tabulated [15] in table 1.

Table 1. Inhibition zone (mm) of the synthesised compounds

Organism Concentrated sample	Gram-positive bacteria				Gram-negative bacteria				Yeasts and Fungi			
	S. aureus (ATCC 25923)		*B. subtilis* (ATCC 6635)		S. typhimurium (ATCC 14028)		E. coli (ATCC 25922)		Candida albicans (ATCC 10231)		Aspergillus fumigatus	
	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml
3a	11	17	16	13	16	18	11	14	24	20	23	26
3b	28	20	22	26	21	24	14	17	30	25	21	32
3c	16	18	27	22	27	26	12	18	42	46	24	28
3d	31	28	26	16	19	25	24	19	35	39	11	13
Standard	36	24	31	28	39	30	43	33	38	36	39	28

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Notes: [a] Chloramphenicol in the case of gram-positive bacteria; cephalothinin the case of gram-negative bacteria and cycloheximide in the case of fungi

2.9. Antifungal activity

Antifungal activity was assigned for the synthetic compounds via active inoculum for experiments according to [16] table 2.

Table 2. Minimal inhibitory concentrations (MIC, µg/mL) of some synthesised compounds

Organism Concentrated sample	Gram-positive bacteria		Gram-negative bacteria		Yeasts and Fungi	
	S. aureus (ATCC 25923)	*B. subtilis* (ATCC 6635)	S. typhimurium (ATCC 14028)	E. coli (ATCC 25922)	Candida albicans (ATCC 10231)	Aspergillus fumigatus
3a	≤45	≤46	–	≤130	≤32	–
3b	≤64	≤66	≤135	≤128	≤34	–
3c	–	–	≤256	–	≤256	–
3d	≤133	≤31	–	–	≤62	–

Notes: [a] Chloramphenicol in the case of gram-positive bacteria; cephalothinin the case of gram-negative bacteria and cycloheximide in the case of fungi

2.10. Minimal inhibitory concentration

Minimal inhibitory concentration (MIC) values of the synthesised compounds were determined using agar dilution technique [17] in table 1.

2.11. Cytotoxicity assay

Cytotoxicity assay according to ATCC by means of Holding organization for natural items and antibodies (VACSERA) [15] in table 3.

Table 3. Antitumor and antioxidant activities for **3a-d**

Dye	Cytotoxicity IC50 µg/L)				Antioxidant activity (ABTS method)		Bleomycin-dependent
	HePG2	HeP2	PC3	MCF-7	Absorbance	Inhibition (%)	DNA damage
3a	>100	>100	>100	92.4	0.070	86.82	0.121
3b	>100	724	>100	96.7	0.089	87.5	0.116
3c	6.87	>100	>100	88.3	0.453	77.65	0.124
3d	8.1	5.6	5.5	6.7	0.065	87.25	0.075
5-fua	8.4	5.1	4.1	5.2	–	–	–
ABTS	–	–	–	–	0.475	0	–
Asc. Acidb	–	–	–	–	0.066	87.38	0.078

2.12. Yellow tetrazolium bromide

Agreement to MTT analyse "Yellow tetrazolium bromide assay" for cell lines were developed to control the inhibition action of thiazolyl- curcumin on growth cell [18].

2.13. Antioxidant activity

In accordance ABTS method, antioxidant activity of thaizolyl- curcumin in spectroscopic grade was assessed [19].

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2.14. Bleomycin-based on DNA damage

The bleomycin is a antibiotics that are established repetitively as antitumor agents [20].The technique that used to assay DNA damage was applied according to [21].

2.15. Dyeing procedure

Thiaolyl-curcumin dyes were evaluated at optimum situations with "dye bath concentration 2 %, liquor ratio 40:1, pH 4and temperature 130°C for 1 hour" [22].

2.16. Fastness testing

According to ISO standard methods for "rubbing, washing, perspiration and light "fastness were applied on the dyed fabrics as revealed in Tables 4 and 5.

Table 4. Fastness properties of the synthesized dyes 3a-d on polyester fabrics

Dyes	Washing				Perspiration							
					Acid				Alkali			
	St*	St**	St***	Alt.	St*	St**	St***	Alt.	St*	St**	St***	Alt.
3a	4	4	4	4-5	4	4	4	4	4	4	4-5	4
3b	4	4	4	4-5	4	4	4	4	4	4	4-5	4
3c	4	4	4	4-5	4	4	4	4	4	4	4-5	4
3d	4	4	4	4-5	4	4	4	4	4	4	4-5	4

Notes: Washing, perspiration, rubbing, St*staining on cotton, St**staining on wool, St***staining on polyester, Alt. Alteration in colour

Table 5. Fastness properties of dyes 3a-d on polyester fabrics

	Rubbing		Sublimation				Light (a)	
			180°C		210°C			
	Dry	Wet	P	C	P	C	(35 h)	(80 h)
3a	3-4	4	3-4	4	3-4	3-4	4-5	5-5
3b	4	4	4	4	4	3-4	5	4-5
3c	4	3-4	4	4	4	4	4-5	5
3d	4	4	4	4	4	3-4	5	5

Notes: a= light fastness, 1-8 scale; rubbing and sublimation fastness, 1-5 scale

Colour assessment

Colour assessment of specimen fabrics were consigned by reflectance spectrophotometer "Gretag Macbeth CE 7000a", fortified with a "D65/108 source and barium sulphate" as standard blank (Table 6).

Table 6. Colour assessments for synthesized dyes on polyester fabrics

Dye no.	K/S	a*	B*	C*	L*	ΔH
3a	64.36	13.7	14.6	24.3	66.8	77.4
3b	62.51	-21.2	16.7	24.9	66.4	67.6
3c	69.43	16.3	11.4	26.8	78.9	78.4
3d	71.55	21.17	18.9	28.3	88.2	89.6

3. Results and discussion

Target compounds were prepared from two step synthesis as shown in Figure 1. By diazotization of aminothiazole derivatives via nitrous acid then followed by coupling with curcumin to afford the corresponding thiazolyl curcumin derivatives **3a-d**.

 doi:10.20944/preprints201811.0011.v1

Thiazolyl curcumin derivatives **3a-d** obtained from the previous reaction gave absorption bands at 194–517 nm in UV spectra. . The UV-vis of **3a-d** explored can be construed in relations of tautomeric. According to polar moiety conducted to azo group, thiazolyl- curcumin derivatives were exhibited four bands with high wavelengths. FTIR spectra showed remarkable bands owing to "O-H, N-H and C=O" were noticed at 3412-3521, 3107-3257 cm^{-1} and 1694-1520 cm^{-1}, Meanwhile, ^{1}H NMR spectrum of **3a** and **3d** displayed signals owed to 6 protons for two OCH_3 (3.68 and 3.62 ppm), Two olifinic protons were exhibited signals at (6.52 and 6.47 ppm) referring to it exist on trans isomers with J_{Value} = 12 Hz.

3.1. Antimicrobial activity

Novel synthesised compounds were evaluated by utilizing disc–agar method. It was measured via inhibition zone diameter determination (Table 1). Thiazolyl curcumin derivatives have been showed good results towards two types of baceria gram positive and gram negative. Examined compounds showed great activity alongside *Candida albicans*. It was seen that **3d** showed greatest antibacterial agent against *"candida albicans"* related to the standard "cycloheximide". MIC values for the newly synthesised thiazolyl- cutcumin were examined against *"Staphylococcus aureus* (ATCC 25,923), *Bacillus subtilis* (ATCC 6,635), *Salmonella typhi*, *Escherichia coli* (ATTC-25922), *and Candida albicans"* compared with "cycloheximide" as standard drug which as in table 2.

3.2. Pharmacological activity

vitro ehrlich ascites was used to determined Antitumor activity [23]. Figure 1 was showed the effect of cytotoxicity for the synthesised thiazolyl- curcumin on four cell lines. Meanwhile, activity of the synthesised compounds was showed variety rang of toxicity (Table 3). Synthesised compounds **3b** and **3d** were displayed top activity**. 3d** exhibited values IC50 8.1, 5.6, 5.5 and 6.7 µg/ mL; in "HePG-2, HeP-2, PC3 and MCF-7" cells. Moreover, **3d** showed higher activity, compound **3b** perceives reasonable activity against "HePG-2, PC3 MCF-7" cells and less activity against HeP-2 cell. The respite compounds were exhibited a variety rang of toxicity.

3.3. Antioxidant activity

Synthesised thiazolyl- curcumin were examined against antioxidant activity to inhibit oxidation in rat brain and kidney homogenates Table III. Compounds **3b** and **3d** were displayed optimal activity against ascorbic acid as reference drug. Consequently, Compound **3a** displayed a reasonable antioxidant activity but **3c** presented poorer activity.

3.4. Bleomycin-dependent DNA damage

Synthesised compounds **3a-d** was showed sensible results to defend DNA damage by bleomycin (table 3). It was remarked that compound 3d revealed high capacity and 3b displayed a moderate capability rather than the other compounds were showed a reasonable activity.

3.5. Structure relationship

One of an imperative area of this work to assign the structure activity relationship (SAR).Refereeing to presence of curcumin moiety in the synthesised structure which is responsible for strong power of antiviral effect towards "hepatocellular carcinoma (liver) HePG-2, mammary gland (breast) MCF-7, Epidermoid carcinoma (larynx) HeP-2 and human (prostate)" cancer. The secret of power activity of curcumin is attributed to it contain two methoxy groups in the para position of the two phenyl groups along the two sides of its structure which contribute to the antiviral effect [24].

3.6. Wash Fastness

As a result of sufficient diffusion of the dyes in the polyester fabrics, the synthesised dyes on fabrics were exhibited good wash fastness regarding to Grey scale[15].

 doi:10.20944/preprints201811.0011.v1

3.7. Perspiration fastness

On agreement with stability of thiazolyl- curcumin dyes to dilapidation in basic and acidic medium were presented a high rating change in colour hue against basic and acidic medium (Table VI).

3.8. Fastness to rubbing

Since, dispersion of dye molecule over the polyester fabrics all of the synthesised thiazolyl-curcumin dyes was revealed good fastness to rubbing. Regarding to colour transferred from the surface of colour fabrics to another surface by rubbing.

3.9. Fastness to sublimation

According to coupling component structure containing curcumin moiety conducted to thaizole ring sublimation fastness showed good results expressed on polyester piece referring to Geometric Grey Scale.

3.10. Light Fastness

Rendering to that the azo compounds were accompanied withthiazolyl rings containing hetero atoms which act as electron-pull are less prone to photo fading [22]. It is observed accountability on the type of electron quantity around hydrazo group. Furthermore, electron electron-pull groups causes increasing of high fastness. This is clearly shown in dye **3d** containing nitro group.

3.11. Colour assessment

Colour assessment and "K/S value" using the Kubelka–Munk equation were assessed for each dyed fabric. Where, K "the absorption coefficient" and S is "the scattering coefficient", R is "the decimal fraction of the reflection of the colour fabric".

$$K/S = [(1-R)^2/2R] - [(1-R_o)^2/2R_o] \quad (1)$$

Until now, corresponding data system was utilized to find miscellaneous shades and to impartiality about the delivery of these shades alongside standard. Furthermore, widely application was derived from colour difference (ΔE) (Rupp et al., 2001), which can be calculated from the CIELAB colour space data. "Lightness (L*), Chroma (C*), hue angle from 0° to 360° (h), (a*)" values were represented. Compounds **3a-d** were displayed a positive results to shift redness Meanwhile, positive results of b* were signified shit to yellowness. The colour spaces "L*, a*, b*" were assigned for measuring the colour strength, and then the colour alteration was designed by

$$\Delta E = L^2 + [(a^2 + b^2)]^{½} \quad (2)$$

Where, ΔE is "the total difference between the sample and the standard", L "the lightness from black (0) to white (100), a* is a red (+)/green (−) ratio and b* is yellow (+)/blue (−)" ratio.

The results were revealed in Table 6 gave the following conclusion: 1) Increasing of K/S value is referred to existence of electron- pull moiety. 2) ΔH*, C* and L* gave +ve values which are responsible for yellow colour, lighter and brighter than the standard. Also, the present study is attentive to presented new eco-friendly disperse dyes with respectable fastness properties and revealing to their pharmacological activity.

4. Conclusions

This work-study concluded synthesis and spectroscopic determination of a novel thiazolyl derivatives **3a-d** including curcumin ring. The spectroscopic techniques' have provided critical

 doi:10.20944/preprints201811.0011.v1

indication that synthetic thiazolyl- curcumin structure was in the right form. Likewise, this study was attentive on the opportunity of evolving novel environment friendly disperse dyes with respectable fastness and presenting glowing pharmacological activity. Moreover, **3d** showed higher activity, compound **3b** perceives reasonable activity against "HePG-2, PC3 MCF-7" cells and less activity against HeP-2 cell. The respite compounds were exhibited a variety rang of toxicity.Finally, Thiazolyl curcumin derivatives have been showed good results towards two types of baceria gram positive and gram negative. Examined compounds showed great activity alongside *Candida albicans*. It was seen that **3d** showed greatest antibacterial agent against *"candida albicans"* related to the standard "cycloheximide".

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Conflicts of Interest: Declare conflicts of interest or state "The authors declare no conflict of interest." Authors must identify and declare any personal circumstances or interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results. Any role of the funders in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript, or in the decision to publish the results must be declared in this section. If there is no role, please state "The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results".

 doi:10.20944/preprints201811.0011.v1

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