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Synthesis of New Heterocycles Incorporating 3-(*N*-phthalimidomethyl)-1,2,4-triazole as Antimicrobial Agents

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A NOVEL series of 1,2,4-triazole Schiff's bases;1,2,4-triazolothiadiazinesand triazolothiadiazoles was prepared from reaction of 4-amino-3-(N-phthalimidomethyl)-1,2,4-triazole-5-thione and different aldehydes, hydrazonyl chlorides, □-haloketones, and substituted benzoic acids. The products have been evaluated for their antimicrobial activity and the Schiff's bases were found to exhibit an antimicrobial activity.

Keywords: Triazole-5-thione, Phthalimide, Schiff's base, Triazolothiadiazine, Triazolothiadiazole and Antimicrobial activity.

In the last few decades, triazoles are reported to exhibit miscellaneous biological properties; *e.g.* antibacterial[1-9],antifungal activity[10], anti-inflammatory[11], anticancer[12,13], antiviral[14,15], antidepressant, and antioxidant properties[16].There are many drugs containing 1,2,4-triazole moiety such as Ribavirin, Rizatriptan, Alprazolam, Fluconazole, and Estazolam (Fig. 1).

Furthermore phthalimide derivatives have been found to possess interesting medicinal and biological properties[17-21].In view of the biological importance mentioned above and in continuation with our previous work in design and discovery of biologically active heterocycles[22-29], we synthesize some new Schiff's bases, triazolo[3,4-*b*]thiadiazoles, and triazolo[3,4-*b*]thiadiazines to screen their antimicrobial activity.

Results and Discussion

Chemistry

The precursor 4-amino-3-1,2,4-triazole-5-thione (1) was prepared from fusion of *N*-phthaloylglycine and thiocarbohydrazide[30]. Treatment of 1 with an equivalent amount of various aldehydes namely, 2-oxo-1,2-dihydroquinoline-3-

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carbaldehyde (2a), tetrazolo [1,5-*a*]quinoline-4-carbaldehyde (2b), 2-chloro-6-methylquinoline-3-carbaldehyde (2c), thiophene-2-carbaldehyde (2d), 2,4-dihydroxybenzaldehyde (2e), and 4-(dimethylamino)benzaldehyde (2f), in absolute ethanol containing 0.5 ml glacial acetic acid under reflux for 3 to 6 hr (TLC) afforded 2-((4-(arylideneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl) methyl) isoindoline-1,3-diones (3a-g) in excellent yields, respectively (Scheme 1). The chemical structures of compounds 3a-g were elucidated by both spectral and elemental analyses. For example, the IR spectra of 3f showed the presence of C=S that resonated at 1170.79cm^{-1}. ^{1}HNMR spectrum of 3f showed a singlet signal at 10.31 ppm corresponding to azamethine proton (N=CH). Moreover, the mass spectrum of 3f showed a molecular ion peak at m/z = 406.06 ($C_{20}H_{18}N_6O_2S$.). Such data proved the synthesis compounds as 3 rather than 3A.

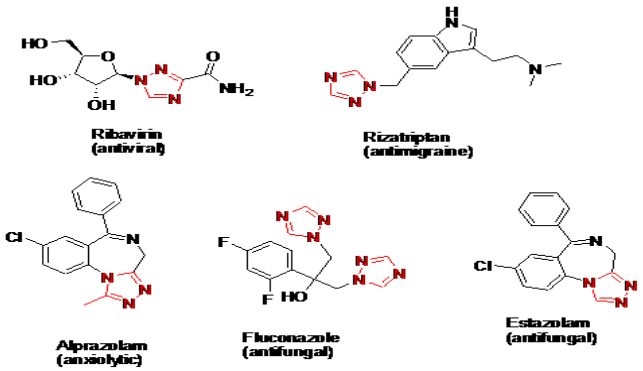
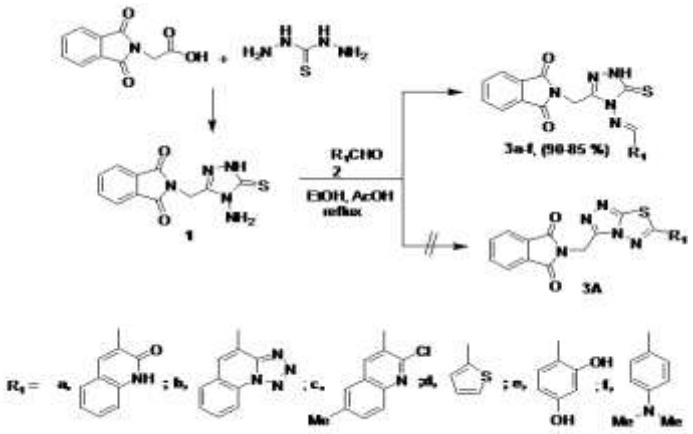


Fig. 1. Some commercial drugs containing pyridine or 1, 2, 4-triazole moiety.

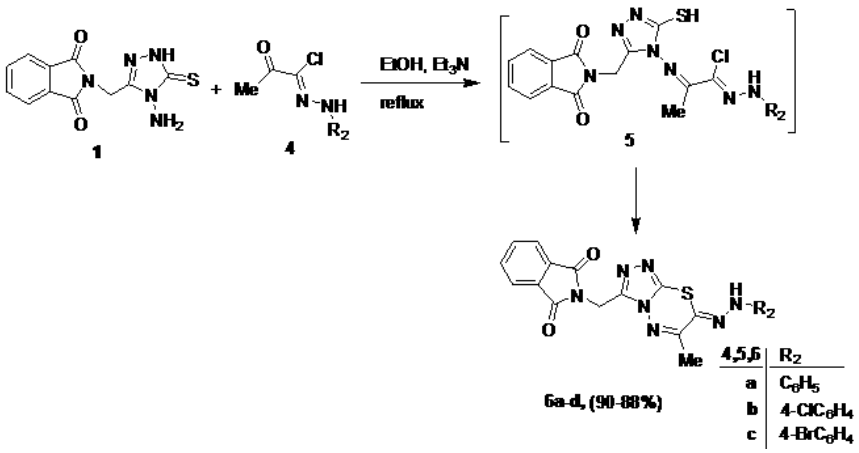


Scheme 1. Synthesis of 1, 2, 4- trazole Schiff's bass 3a-f.

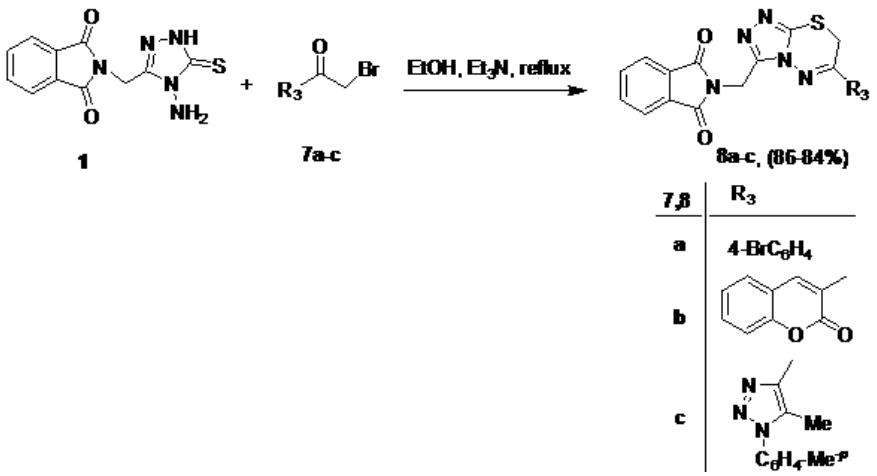
Reaction of compound 1 with hydrazonoyl chlorides 4a-c, namely 2-oxo-N'-phenylpropanehydrazonoyl chloride (4a), N'-(4-chlorophenyl)-2-oxopropanehydrazonoyl chloride (4b), N'-(4-bromophenyl)-2-oxopropanehydrazonoyl chloride (4c) and 2-oxo-N'-*p*-tolylpropanehydrazonoyl chloride (4d),in ethanol in the presence of triethyl amine as a catalyst, under reflux conditions afforded 6-methyl-7-(2-arylhydrazono)-7*H*- [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazine derivatives 6a–d,in excellent yields, respectively (Scheme 2).

The IR spectrum of compound 6 showed no absorption bands for NH_2 and C=S. ^{1}HNMR spectra of 6a-dshowed a singlet signal within the 2.33-2.38 ppm region which assigned for the methyl protonson C_5. The structures of 6 were confirmed further by the mass spectroscopy. Clearly, both C=S and NH_2groups were involved in cyclization reaction to give thiadiazine ring.

On the same fashion, by analogous procedure substituted-7H-[1,2,4] triazolo [3,4-b][1,3,4] thiadiazines (8a-c), were obtained in excellent yields, from reaction 1with equimolar amount α-haloketones (7a-c) (4-brmophenacyl bromide (7a), 3-bromoacetylcoumarin (7b), and 2-bromo-1-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl) ethanone (7c) in absolute ethanol under reflux (Scheme 3). The 1HNMR spectra of 8a-c showed a singlet signal at 4.22-4.35 ppm region due to methylene protonson C6 of thiadiazine ring.

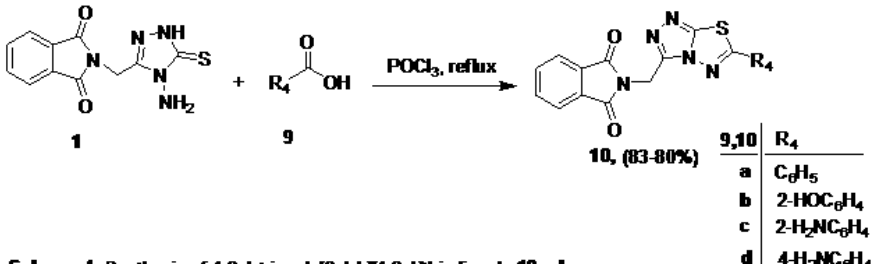


Scheme 2. Synthesis of 1, 2, 4-triazolo [1, 3, 4] thiadiazine 6a-d.



Scheme 3. Synthesis of 1, 2, 4-triazolo [3, 4-b] [1, 3, 4]thiadiazine 8a-c.

The investigation was next extended to synthesize triazolothiadiazole derivatives. Compound 1 was treated with substituted benzoic acid (9a-d) in phosphours oxychloride under reflux to afford 2-((6-aryl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)isoindoline-1,3-diones (10a-d), in good yields, respectively (Scheme 4).



Scheme 4. Synthesis of 1, 2, 4-triazolo [3, 4-b] [1, 3, 4]thiadiazine 10a-d.

Antimicrobial activity

The antimicrobial activity of the synthesized compounds was screened against two Gram positive, two Gram negative bacteria, and one fungus by using ampicillin and clotrimazoleas standards. Upon exploration of antimicrobial data (Tables 1 and 2) triazolothiadiazole derivatives (10a-d) showed moderate to good activity against Gram negative bacteria but they displayed no activity against Gram positive bacteria. Triazolo[3,4-*b*][1,3,4]thiadiazines (6a & 6d) have a good activity against Gram negative bacteria. In addition, compounds 8b, 8c**,** 8a and 8b showed

high activity against *E. coli* and *Staphylococcus aureus*, *B. subtilis*, respectively. Shiff's base derivatives (3a>3b>3f>3e>3c>3d) displayed an excellent activity against all tested bacteria with inhibition zones and activity index ranged from 17 to 23 mm and ~ 77.3-95.8%, respectively. The most active compounds are 3a, 3b and 3f with inhibition zones and minimum inhibitory concentration (MIC) ranged between 19 to 23 mm and 62.5 to 250µg/ml, respectively (Table 2).Antifungal screening revealed that Schiff's bases 3c, 3e, and 3d have significant antimycotic activity with inhibition zones of 17,15 14 mm, respectively, while, compounds 3a, 3f > 3b were the most active with inhibition zones as 20, 20, and 19 mm and MIC as 15.6, 31.25, and 187.5µg/ml, respectively. Other compounds showed poor activity against *C. Albicans* (Tables 1 and 2).

TABLE 1. *In vitro* antimicrobial activity of the synthesized compounds[a,b].

Entry	Gram negative bacteria				Gram positive bacteria				Fungi	
	E. coli		*Pseudomonas aeuroginosa*		*Staphylococcus aureus*		*B. subtilis*		*C. Albicans*	
	I.Z.	% A.I.	I.Z.	% A.I.	I.Z.	%A.I.	I.Z.	% A.I.	I.Z.	%A.I.
1	3	13.0	9	37.5	8	36.4	10	41.7	NA	----
3a	22	95.6	21	87.5	20	90.9	22	91.6	20	80.0
3b	21	91.3	22	91.7	19	86.4	23	95.8	19	76.0
3c	19	82.6	20	83.3	17	77.3	16	66.7	17	68.0
3d	18	78.3	19	79.2	16	72.7	21	87.5	14	56.0
3e	18	78.3	21	87.5	19	86.4	20	83.3	15	60.0
3f	21	91.3	19	79.2	20	90.9	20	83.3	20	80.0
6a	15	65.2	14	58.4	16	72.7	16	66.7	NA	----
6b	13	56.5	11	45.8	10	45.5	9	37.5	NA	----
6c	14	60.9	10	41.7	11	50.0	8	33.3	NA	----
6d	16	69.6	15	62.5	16	72.7	5	20.8	NA	----
8a	12	52.2	7	29.2	17	77.3	16	66.7	NA	----
8b	17	73.9	13	54.2	16	72.7	17	70.8	NA	----
8c	19	82.6	11	45.8	10	45.4	10	41.7	3	12.0
10a	11	47.8	12	50.0	NA	----	NA	-----	NA	----
10b	15	65.2	15	62.5	NA	----	14	58.3	5	20.0
10c	16	69.9	14	58.4	NA	----	NA	----	NA	----
10d	12	52.2	13	54.2	NA	----	NA	----	NA	----
Ampicillin	23	100	24	100	22	100	24	100	NA	----
Clotrimazole	NA	----	NA	----	NA	----	NA	----	25	100

[a]Antimicrobial activity expressed as inhibition diameter zones (IZ) in millimeters (mm) of synthesized compounds against the pathological strains based on well diffusion assay; [b]The experiment was carried out in triplicate and the average zone of inhibition was calculated; [c]A.I. activity index ; [e]NA No activity.

TABLE 2. Antimicrobial and Antimycotic Activities in terms of MIC (µg/ml)

C. Albicans	*Bacillus subtilis*	*S. aureus*	*Pseudomonas aeuroginosa*	*E. coli*	Entry
15.6	125	93.7	93.7	93.7	**3a**
31.25	250	125	187.5	125	**3b**
187.5	125	125	93.7	125	**3c**
125	250	187.5	93.7	93.7	**3d**
31.25	125	250	187.5	93.7	**3e**
187.5	250	125	62.5	187.5	**3f**
----	250	187.5	187.5	125	Ampicillin
7.8	----	----	----	----	Clotrimazole

Experiment

Chemistry

Melting points were determined on digital Gallen-Kamp MFB-595 instrument using open capillary tubes and are uncorrected. IR spectra were recorded on a Schimadzu FTIR 440 spectrometer using KBr pellets. Mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Shimadzu model (500 MHz) Ultra Shield NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ ppm units. The elemental analyses (% C, H, N) were done at the Microanalytical Center, Cairo University, Cairo, Egypt. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC aluminum sheets silica gel 60 F_{254} (Merck).2-bromo-1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanone **7c**[31]was prepared according to the literature.

General procedure for synthesis of Schiff's bases 3a-f

A mixture of 4-aminotriazole (1) (1 mmol, 0.274 g), and appropriate aromatic aldehydes (2a-f) (1 mmol) in EtOH (20 ml) containing glacial acetic acid (0.5 ml) was heated under reflux from 3 to 6 hr (TLC). The precipitate formed was collected by filtration, washed with EtOH.

2-((4-((2-oxo-1,2-dihydroquinolin-3-yl)methyleneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3a)

Yield 92%, Yellow crystals, m.p. 259-260°C. IR (cm^{-1}): *v* 3291 (NH), 3271 (NH), 1771, 1726,1709(3C=O, cyclic amide), 1647 (C=N), 1120 (C=S); ^{1}H NMR (DMSO-d_6): δ_H 5.00 (s, 2H, CH_2), 7.28 (dt, 2H, *J* = 7.7 Hz, Ar-H), 7.73 (d, 2H, *J* = 7.7Hz, Ar-H), 7.88 (m, 4H, Ar-H), 8.58 (s, 1H, quinoline-H), 10.31 (s, 1H, N=CH), 12.23 (s, D_2O exchangeable, 1H, NH), 14.02 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ_c 32.9(CH_2), 123.9, 125.5, 126.2, 128.1, 129.1, 131.5, 131.8, 132.3, 133.2, 135.3 (Ar-C), 152.0 (N=CH), 153.2 (C=N), 158.5

(C=O), 164.4(C=O), 177.5(C=S). E1-MS: (*m/z*, %):430.08 (M^+, 65), Anal. Calc. for $C_{21}H_{14}N_6O_3S$ (430.439): C, 58.60; H, 3.28; N, 19.52. Found: C, 58.48; H, 3.24; N, 19.30.

2-((4-(tetrazolo[1,5-a]quinolin-4-ylmethyleneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3b)

Yield 90%, Yellow crystals, m.p. 280-281°C. IR (cm^{-1}): *v* 3273.25 (NH), 1774.51, 1728.22 (2C=O, cyclic amide), 1618.28 (C=N), 1116.78 (C=S); ^{1}H NMR (DMSO-d_6): δ_H 4.98 (s, 2H, CH_2), 7.28 (d, 2H, *J* = 7.65 Hz, Ar-H), 7.73 (d, 2H, *J* = 7.65 Hz, Ar-H), 7.82 (m, 4H, Ar-H), 8.63 (s, 1H, quinoline-H), 10.41 (s, 1H, N=CH), 13.94 (s, D_2O exchangeable, 1H, NH); ^{13}C NMR (DMSO-d_6) δ_c 33.65 (CH_2), 124.05, 125.72, 126.97, 128.13, 129.10, 131.52, 131.81, 132.29, 133.23, 135.33 (Ar-C), 152.02 (N=CH), 153.23 (C=N), 158.54, 164.39 (2C=O), 177.47 (C=S); E1-MS (*m/z*, %) 455 (M^+, 60): Anal. Calc. for $C_{21}H_{13}N_9O_2S$: Calculated: C, 55.38; H, 2.88; N, 27.68. Found: C, 55.32; H, 2.66; N, 27.50.

2-((4-((2-chloro-6-methylquinolin-3-yl)methyleneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3c)

Yield 93%, Green crystals, m.p.257-258°C. IR (cm^{-1}): *v* 3250 (NH), 1772.58, 1728.22 (2C=O, cyclic amide), 1620.30 (C=N), 1119.77 (C=S). ^{1}H NMR (DMSO-d_6): δ_H 3.22 (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 7.38-7.98 (m, 7H, Ar-H), 8.58 (s, 1H, quinoline-H), 10.23 (s, 1H, N=CH), 13.87 (s, D_2O exchangeable, 1H, NH); E1-MS: (*m/z*, %) 462.06 (M^+, 70); Anal. Calc. for $C_{22}H_{15}ClN_6O_2S$ (462.912): C, 57.08; H, 3.27; N, 18.15. Found: C, 56.97; H, 3.3; N, 17.87.

2-((4-(thiophen-2-ylmethyleneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3d)

Yield 93%, Pale yellow, m.p.245-246°C. IR (cm^{-1}): *v* 3237.55 (NH), 1776.44, 1724.36 (C=O, cyclic amide), 1600.92 (C=N), 1117.67 (C=S); ^{1}H NMR (DMSO-d_6): δ_H 5.01 (s, 2H, CH_2), 7.076 (dd, 1H, *J* = 5 Hz, 3.5 Hz, thiophen-H), 7.199 (dd, 1H, *J* = 3.5 Hz, 1 Hz, thiophen-H), 7.531 (dd, 1H, *J* = 5 Hz, 1 Hz, thiophen-H),7.82 (m, 4H, Ar-H), 9.54 (s, 1H, N=CH), 13.86 (s, D_2O exchangeable, 1H, NH); E1-MS: (*m/z*, %) 369.04 (M^+, 57); Anal. Calc. for $C_{16}H_{11}N_5O_2S_2$ (369.42): C, 52.02; H, 3.00; N, 18.96. Found: C, 52.98; H, 2.97; N, 18.67.

2-((4-(2,4-dihydroxybenzylideneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3e)

Yield 90%, Pale yellow crystals, m.p. 279-280°C. IR (cm^{-1}): *v* 3420 (OH), 3107.32 (NH), 1778.37, 1701.22 (C=O, cyclic amide), 1629.85 (C=N), 1165.55 (C=S). ^{1}H NMR (DMSO-d_6): δ_H 5.09 (s, 2H, CH_2), 6.65 (d, 1H, *J* = 8.4 Hz, Ar-H),7.73 (s, 1H, Ar-H), 7.82 (dd, 1H, *J* = 8.4 Hz, Ar-H), 8.84 (m, 4H, Ar-H), 9.57 (s, 1H, N=CH), 10.55 (s, D_2O exchangeable, 1H, OH), 11.75 (s, D_2O exchangeable, 1H, OH) 13.89 (s, D_2O exchangeable, 1H, NH); E1-MS: (*m/z*, %) 395 (M^+, 20); Anal. Calc. for $C_{18}H_{13}N_5O_4S$ (395.39): C, 54.68; H, 3.31; N, 17.71 Found: C, 54.45; H, 3.11; N, 17.43.

2-((4-(4-(dimethylamino)benzylideneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)isoindoline-1,3-dione (3f)

Yield 93%, Yellow crystals, m.p. 262-263^{o}C. IR (cm^{-1}): *v* 1772.58, 1728.22 (C=O, cyclic amide), 1614.42 (C=N), 1170.79 (C=S). ^{1}H NMR (DMSO-d$_6$): δ_H 3.37 (s, 6H, 2CH$_3$), 5.13 (s, 2H, CH$_2$), 6.69 (d, 2H, *J* = 8.65 Hz, Ph), 7.45 (d, 2H, *J* = 8.65 Hz, Ar-H), 7.82 (m, 4H, Ar-H), 9.32 (s, 1H, N=CH), 13.84 (s, D$_2$O exchangeable, 1H, NH); E1-MS: (*m/z*, %): 406.06 (M$^+$, 7); Anal. Calc. for $C_{20}H_{18}N_6O_2S$: C, 59.10; H, 4.46; N, 20.68 Found: C, 59; H, 4.28; N, 20.35.

General procedure for synthesis of 6a-d

A mixture of compound 1 (1 mmol, 0.274 g) and hydrazonyl chloride (3a-d)(1 mmol) in absolute EtOH (30 ml) containing Et$_3$N (5 drops) was heated under reflux form 4 to 5 hr (TLC). The precipitate formed was collected by filtration, washed with EtOH.

2-((6-methyl-7-(2-phenylhydrazono)-7H-[1,2,4]triazolo[3,4b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (6a).

Yield 90%, Yellow crystals, m.p. 283-284^{o}C. IR (cm^{-1}): *v* 3180.62 (NH), 1770.65, 1718.58 (2C=O, cyclic amide), 1610.40 (C=N); ^{1}H NMR (DMSO-d$_6$): δ_H 2.33 (s, 3H, CH$_3$), 4.99 (s, 2H, CH$_2$), 6.92-7.29 (m, 5H, Ar-H), 7.92 (m, 4H, Ar-H), 10.81(s, D$_2$O exchangeable, 1H, NH); E1-MS: (*m/z*, %) 417.05 (M$^+$, 68); Anal. Calc. for $C_{20}H_{15}N_7O_2S$: C, 57.54; H, 3.62; N, 23.49. Found: C, 57.48; H, 3.46; N, 23.30.

2-((7-(2-(4-chlorophenyl)hydrazono)-6-methyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (6b)

Yield 88%, Yellowish green, m.p. 300^{o}C. IR (cm^{-1}): *v* 3209.55 (NH), 1774.51, 1724.36 (C=O, cyclic amide), 1600.92 (C=N); ^{1}H NMR (DMSO-d$_6$): δ_H 2.38 (s, 3H, CH$_3$), 5.03 (s, 2H, CH$_2$), 7.25 (d, 2H, J = 9 Hz, Ar-H), 7.46 (d, 2H, J = 9 Hz, Ar-H), 7.89 (m, 4H, Ar-H), 10.53 (s, D$_2$O exchangeable, 1H, NH); E1-MS: (*m/z*, %) 451.03 (M$^+$, 57); Anal. Calc. for $C_{20}H_{14}ClN_7O_2S$: C, 53.16; H, 3.12; N, 21.70. Found: C, 53.00; H, 2.96; N, 21.49.

2-((7-(2-(4-bromophenyl)hydrazono)-6-methyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (6c)

Yield 88%, Yellow powder m.p.>300^{o}C. IR (cm^{-1}): *v* 3207.62 (NH), 1778.37, 1724.36 (C=O, cyclic amide), 1615.60 (C=N); ^{1}H NMR (DMSO-d$_6$): δ_H 2.36 (s, 3H, CH$_3$), 5.03 (s, 2H, CH$_2$), 7.25 (d, 2H, *J* = 9.15 Hz, Ar-H), 7.46 (d, 2H, *J* = 9.15 Hz, Ar-H), 7.89 (m, 4H, Ar-H),10.35 (s, D$_2$O exchangeable, 1H, NH); EI-MS: (*m/z*, %), 496.93 (M$^+$, 34); Anal. Calc. for $C_{20}H_{14}BrN_7O_2S$: C, 48.40; H, 2.84; N, 19.75. Found: C, 48.23; H, 2.61; N, 19.53.

2-((6-methyl-7-(2-p-tolylhydrazono)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (6d)

Yield 89%, Yellow powder, m.p. 290-291^{o}C. IR (cm^{-1}): *v* 3209.55 (NH), 1774.51, 1724.36 (C=O, cyclic amide), 1610.56 (C=N); ^{1}H NMR (DMSO-d$_6$): δ_H 2.36 (s, 3H,

CH_3), 2.44 (3H, CH_3), 5.02 (s, 2H, CH_2), 6.98 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.22 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.89 (m, 4H, Ar-H),10.33 (s, D_2O exchangeable, 1H, NH); EI-MS: (*m/z*, %), 431.07 (M^+, 56); Anal. Calc. for $C_{21}H_{17}N_7O_2S$: Calculated: C, 58.46; H, 3.97; N, 22.72. Found: C, 58.33; H, 3.79; N, 22.57.

General procedure for synthesis of 8a-c

To a solution of compound 1 (1 mmol, 0.274 g) in absolute EtOH (40 ml), α-haloketones (7a-c) (1 mmol) was added. The mixture was heated at reflux temperature for 3-4 hr (TLC), then the reaction mixture was allowed to cool at room temperature, filtered off, washed with EtOH.

2-((6-(4-bromophenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (8a)

Yield 86%, pink crystals, m.p. 225-226°C, IR (cm^{-1}): *ν* 1774.51, 1730.15 (C=O, cyclic amide), 1585.49 (C=N); ^1H NMR (DMSO-d_6): δ_H 4.35 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 7.72-7.91 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6) δ_c 23.28 (CH_2), 32.8 (CH_2), 123.97, 126.42, 129.96, 131.99, 132.50, 132.94, 135.36 (Ar-C), 141.95, 148.88, 155.03 3(N=C), 153.23 (C=N), 167.63 (C=O); EI-MS: (*m/z*, %), 455 (M^+, 8); Anal. Calc. for $C_{19}H_{12}BrN_5O_2S$: Calculated: 50.23; H, 2.66; N, 15.42 Found: C, 50.04; H, 2.49; N, 15.28.

2-((6-(2-oxo-2H-chromen-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (8b)

Yield 84%, pink crystals, m.p. 222-223° C, IR (cm^{-1}): *ν* 1770.65, 1724.36 (C=O, cyclic amide), 1608.63 (C=N); ^1H NMR (DMSO-d_6): δ_H 4.22 (s, 2H, CH_2), 5.07 (s, 2H, CH_2), 7.52-7.86 (m, 8H, Ar-H & coumarin-H); EI-MS: (*m/z*, %), 443.09 (M^+, 5); Anal. Calc. for $C_{22}H_{13}N_5O_4S$: Calculated: C, 59.59; H, 2.95; N, 15.79 Found: C, 59.32; H, 2.73; N, 15.51.

2-((6-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)methyl)isoindoline-1,3-dione (8c)

Yield 85%, yellow, m.p. 260-261° C, IR (cm^{-1}): *ν* 1770.65, 1720.50 (C=O, cyclic amide), 1606.70 (C=N); ^1H NMR (DMSO-d_6): 2.36, 2.43 (s, 6H, $2CH_3$), δ_H 4.32 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 7.42-7.83 (m, 8H, Ar-H); EI-MS: (*m/z*, %), 470 (M^+, 9); Anal. Calc. for $C_{23}H_{18}N_8O_2S$: Calculated: C, 58.71; H, 3.86; N, 23.82 Found: C, 58.59; H, 3.63; N, 23.55.

General procedure for synthesis of 10a-d

A mixture of 1 (1 mmol, 0.274 g) and substituted aromatic acid (9a-d) (1 mmol) in $POCl_3$ (10 ml) was refluxed for 6 hr the mixture was cooled to room temperature, poured onto crushed ice with stirring, then K_2CO_3 soln. was added till the pH of the mixture was raised to 8 to remove the excess $POCl_3$, the mixture was stand overnight and the solid separated out was filtered and washed with water.

2-((6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)isoindoline-1,3-dione (10a)

Yield 82%, Brown solid, m.p. 243-244^{o}C. IR (cm^{-1}): *v* 1774.51, 1714.27 (C=O, cyclic amide), 1600 (C=N); ^{1}H NMR (DMSO-d_6): δ_H 5.28 (s, 2H, CH_2), 7.53-7.94 (m, 9H, Ar-H); EI-MS: (*m/z*, %), 361.17 (M^+, 55); Anal. Calc. for $C_{18}H_{11}N_5O_2S$: Calculated: C, 59.82; H, 3.07; N, 19.38 Found: C, 59.67; H, 2.96; N, 19.26.

2-((6-(2-hydroxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)isoindoline-1,3-dione (10b)

Yield 80%, Pink crystals, m.p. 218-219^{o}C. IR (cm^{-1}): *v* 3435.22 (OH), 1774.51, 1716. 65 (C=O, cyclic amide), 1600.92 (C=N); ^{1}H NMR (DMSO-d_6): δ_H 5.28 (s, 2H, CH_2), 7.17-7.93 (m, 8H, Ar-H), 10.35 (s, D_2O exchangeable, 1H, OH). EI-MS: (*m/z*, %), 377.15 (M^+, 60); Anal. Calc. for $C_{18}H_{11}N_5O_3S$: Calculated: C, 57.29; H, 2.94; N, 18.56 Found: C, 57.11; H, 2.79; N, 18.37.

2-((6-(2-aminophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)isoindoline-1,3-dione (10c)

Yield 81%, brown solid, m.p. 277-278^{o}C. IR (cm^{-1}): *v* 3448.72, 3433.29 (NH_2), 1774.51, 1720.50 (C=O, cyclic amide), 1660.71, 1608.63(C=N); ^{1}H NMR (DMSO-d_6): δ_H 5.21 (s, 2H, CH_2), 5.26 (s, D_2O exchangeable, 2H, NH_2), 7.15-7.69 (m, 8H, Ar-H); EI-MS: (*m/z*, %), 376.10 (M^+, 55); Anal. Calc. for $C_{18}H_{12}N_6O_2S$: Calculated: C, 54.44; H, 3.21; N, 22.33 Found: C, 54.28; H, 3.01; N, 22.02.

2-((6-(4-aminophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)isoindoline-1,3-dione(10d)

Yield 83%, brown m.p. 240-242^{o}C. IR (cm^{-1}): *v* 3358.07, 3228.84 (NH_2), 1772.58, 1718.58 (2C=O, cyclic amide), 1602.85 (C=N); ^{1}H NMR (DMSO-d_6): δ_H 5.16 (s, 2H, CH_2), 5.18 (s, D_2O exchangeable, 2H, NH_2), 6.95 (d, 2H, J = 8.5 Hz, Ph), 7.65-7.89 (m, 6H, Ar-H); EI-MS: (*m/z*, %), 376.10 (M^+, 60); Anal. Calc. for $C_{18}H_{12}N_6O_2S$: Calculated: C, 54.44; H, 3.21; N, 22.33 Found: C, 54.19; H, 3.05; N, 22.10.

Antimicrobial evaluation

The In vitro antimicrobial activity of the synthesized compounds against a panel of gram positive *Staphylococcus aureus*, *Bacillus subtilis*, gram negative *Escherichia coli*, *Pseudomonas aeuroginosa* bacterial and *Candida albicans* was determined using agar well diffusion method as described in the literature[(32)]and the result was cited in Tables 1 and 2.

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تشييد مشتقات حلقية غير متجانسة جديدة محتوية على 3 - (فثالميد اثيل) -1،2،4- تيرايازول كمضادات للميكروبات

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توضح الدراسات العلمية السابقة ان مشتقات التيرايازول تتمتع بخواص بيولوجية و صيدلانية عالية فهى تمتلك على سبيل المثال خواص مضادات البكتريا و الفطريات و الحساسية و كذلك كمضادات لبعض انواع السرطان. أيضا مركبات الفثالميد تتميز بخواص بيولوجية عالية. و من هذا المنطلق تم تحضير مركبات جديدة تحتواتى على نواتى الفثالميد و التيرايزول. تم تحضير المادة البادئة 4-امينو-3-(1،2،4-)-تيرايازول-5-ثايون بتفاعل فثالويل جليسين مع الثيو كربوهيرازيد. تتفاعل المادة البادئة مع مجموعة مختلفة من الكواشف مثل الالدهيدات و الفناثيل بروميدات و كلوريدات الهيدرازونات لتعطى مشتقات جديدة من الاريلدين امينات و التيرازولوثياديازين و جمعيهم يحتوى على حلقتى الفثالميد و التيرايزول. تم اجراء مسح بيولوجى لجميع المركبات الجديدة كمضادات للبكتريا و الفطريات و اظهرت النتائج فعالية ملموسة تجاه معظم انواع الميكروبات.