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SYNTHESIS AND BIOLOGICAL STUDY OF SOME SCHIFF BASES AND THEIR THIAZOLIDINONE DERIVATIVES

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ABSTRACT

Heterocyclic compounds play an important role in medicinal chemistry. Motifs such as triazoles, pyrazoles, oxazoles, imidazoles, thiazoles, etc are routinely observed in several compounds of pharmacological interest. These paper my effort on the development of the synthesis of some novel functionalized heterocyclic compounds as potent antibacterial agents. The biological evaluation of these synthetic derivatives showed some promise as antibacterial agents.

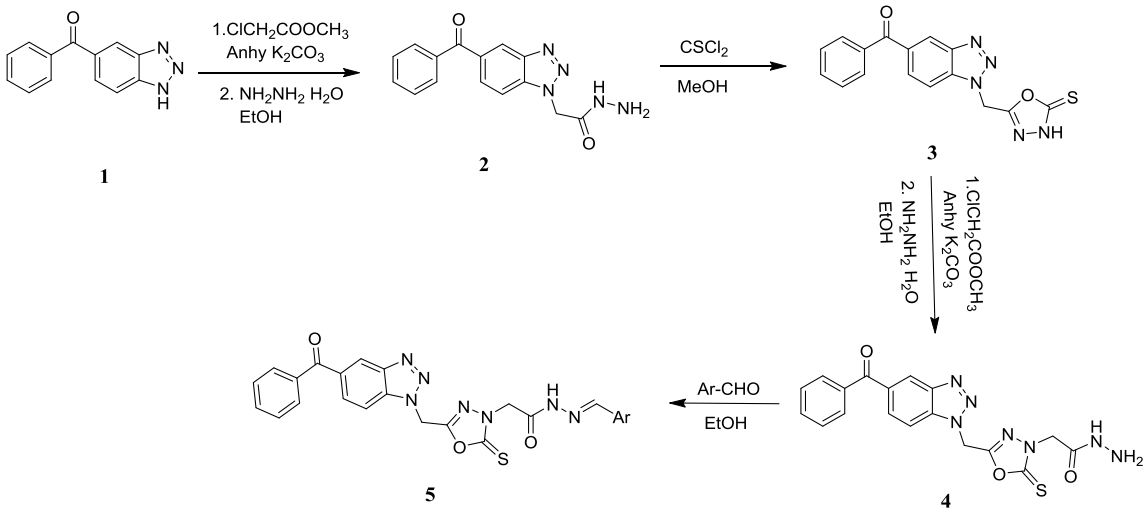
KEYWORDS: Schiff base, thiazolidinones, microbial, medicinal chemistry.

1. INTRODUCTION

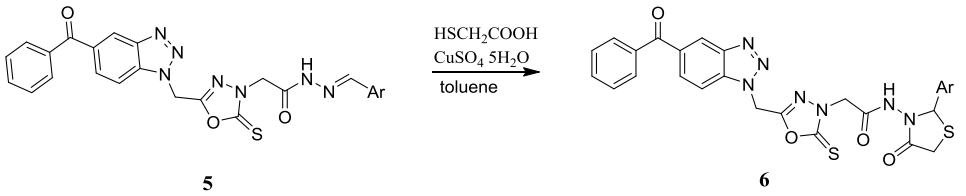
Heterocyclic compounds are the substantial part of the chemical and pharmaceutical sciences. Heterocyclic compounds have a very important place in the biological structure. Heterocyclic compounds also exist in a huge diversity of drug compounds[1] for examples antibiotic, antitumor, antiviral, antibacterial, antifungal etc. These molecules are also found to be very useful intermediates for the making of a number of heterocyclic compounds.[2] 4-Thiazolidinones are very important structural units of pharmaceutical importance.[3] Thiazolidine-4-one and its derivatives have been employed for photography as synthetic intermediates, dyes and show distinct biological properties such as antiarthritic, antibacterial, anti-inflammatory, antidiabetic and a calcium antagonist.[4,5,6,7] Many synthetic methods for 4-thiazolidinediones are stated in the literature One-pot three-component reaction by cyclocondensation of amines, carbonyls and thioglycolic acid or its derivatives has been broadly employed as a synthetic path for 4- thiazolidinones.[8]

2. RESULTS AND DISCUSSION

2.1 Chemistry



Scheme 1. The synthesis of compounds 1-5a-e.



Where, Ar = C_6H_5- , p-Cl C_6H_4-, p-$CH_3C_6H_4$-, p-$OCH_3C_6H_4$-, 2-thienyl

Scheme 2. The synthesis of compounds 5a-e -6a-e.

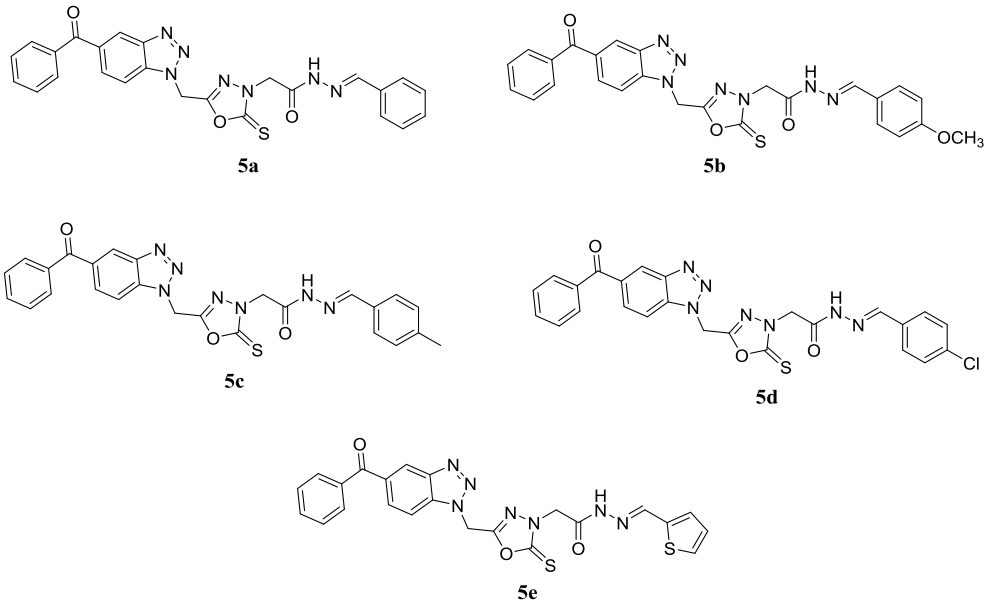


Fig. 1 Synthesized Schiff base compounds.

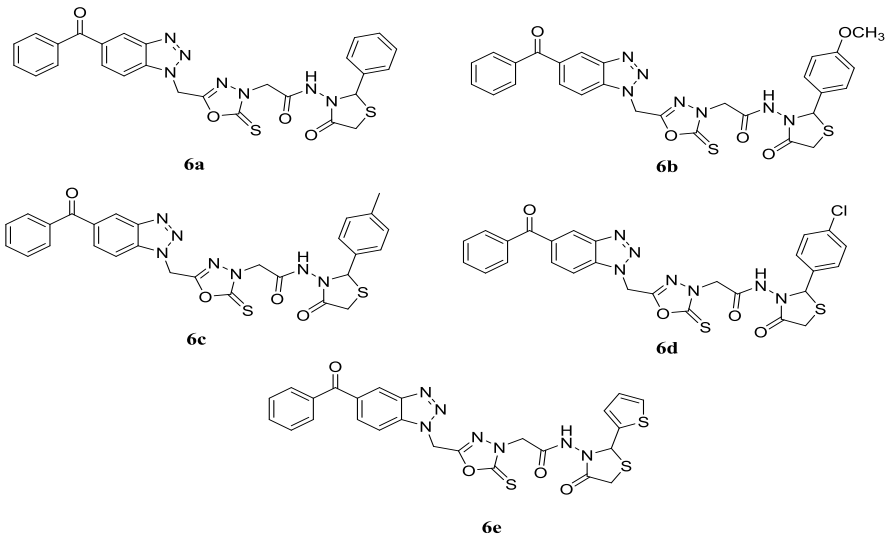


Fig. 2: synthesized thiazolidinone derivatives.

3. Biological evaluation

All newly synthesized molecules fig.1 and fig.2 were inspected for antibacterial activity against two gram +ve bacterial strains (*Staphylococcus aureus* MTCC 96, *Bacillus cereus* MTCC 430), two gram -ve bacterial strains (*Pseudomonas aeruginosa* MTCC 741, *Klebsiella pneumoniae* MTCC 109) and two fungal strains (*Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 282) utilizing the agar dilution method.[9] In this place, Ampicillin and Chloramphenicol were employed as a standard control drug for antibacterial potency, where as Griseofulvin and Nystatin were employed as a standard drug for antifungal study. In order to evaluate minimum inhibitory concentration, a stock solution of the synthesized molecules (2000 µg/mL) were planned in DMSO and after that audit molecule was included in a stated amount of molten sterile agar, i.e. dextrose agar and nutrient agar for fungal and antibacterial study respectively.

3.1 In vitro antibacterial activity

3.1.1 Determination of minimum inhibitory concentration (MIC). The sterile test tubes holding 1ml of sterile media were added to 1ml of different serially diluted study samples. To these tubes, 0.1ml of suspension of respective microorganism was added in normal saline and incubated at ~37C for 24hr. After 24hr a loop full of samples was streaked in a zigzag pattern over the agar medium in a Petri plate from the culture and this was incubated at ~37C for 24hr. Then the lowest concentration of the sample that inhibited the microbial growth in the petri dish was examined and this is considered as MIC. This method was utilized to prove the MIC. The outcomes are outlined in Table 1.

Table 1: ***Results of in vitro antibacterial activity.***

Minimum inhibition concentration (ug/mL)					
Sr.#	**Compound #**	**E.Coli MTCC 443**	**P.Aeruginosa MTCC 1688**	**S.Aureus MTCC 96**	**S.Pyogenus MTCC 442**
1.	5a	230	120	100	260
2.	5b	200	80	200	260
3.	5c	180	200	90	200
4.	5d	60	125	100	180
5.	5e	100	250	170	170
6.	6a	210	130	250	135
7.	6b	200	190	120	50
8.	6c	170	100	230	80
9.	6d	75	210	200	50
10.	6e	100	200	70	200
Std.1	Ampicillin	100	100	250	100
Std.2	Chloramphenicol	50	50	50	50

3.2 In vitro antifungal activity

3.2.1 Determination of minimum inhibitory concentration (MIC). The inoculums were formulated by catching a loopful of stock culture to about 100mL of nutrient broth, in 250 mL clean and sterilized conical flask. The flasks were incubated at 27ºC for 24hr before use. The plates were kept aside for about 2hrs at room temperature to allow diffusion of the solution uniformly, into potato-dextrose-agar medium. Then the plates were incubated at 25ºC for 48hrs. The topmost dilution appearing at least 99% inhibition zone is considered as MIC. The result of this is more affected by the size of the inoculum. The results of antifungal activity are demonstrated in Table 2.

Table 2: ***Results of in vitro antifungal activity.***

Minimum inhibition concentration (ug/mL)				
Sr.#	**Compound #**	**C. Albicans MTCC 227**	**A.Niger MTCC 282**	**A.Clavatus MTCC 96**
1.	5a	1000	1000	700
2.	5b	1000	1000	900
3.	5c	800	500	1000
4.	5d	350	800	>1000
5.	5e	400	800	>1000
6.	6a	>1000	>1000	>1000
7.	6b	>1000	>1000	>1000
8.	6c	1000	>1000	>1000
9.	6d	900	>1000	>1000
10.	6e	500	1000	1000
Std.1	Nystatin	100	100	100
Std.2	Griseofulvin	500	100	100

3.3 Antibacterial and antifungal activity results

The antibacterial activity of the synthesized molecules 5a-e and 6a-e were examined in-vitro utilizing broth dilution process against four micro-organisms viz. E. coli, P. aeruginosa, S. pyogenus and S. aureus. Table 1 show that all novel developed molecules found to exhibit good to moderate activity against the specific microbial strain. The antifungal study of synthesized molecules were examined in vitro utilizing an agar plate procedure against the three strain listed in Table 2 at distinct concentration ranging between 100ug/mL to 1200 µg/mL. Out of which 5d, 5e and 6e shoes activity against C.albicans at concentration 350, 400, and 500 µg/mL respectively.

4. Experimental

4.1 Materials

All the reactants were of reagent grade, and purchased from Acros Organics, Alfa Aesar or Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific.

4.2 Instrumentation

Melting points were determined in open capillary tubes in a Buchi 510 circulating oil apparatus and are uncorrected. Nuclear Magnetic Spectroscopy (NMR) NMR spectra were produced using the Varian 300 MHz spectrophotometer. The instrument was maintained at 25^{o} C operating at 300 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. The deuterated solvent ($CDCl_3$, DMSO-d_6) used for each respective spectrum is referenced to the appropriate literature peak shift.

4.3 General Procedure for the synthesis of compound.[10,11] 2 To the solution of reactant 1 (1eq.) in absolute Methanol (60ml), methylchloroacetate (1eq.), hydrazine monohydrate and anhydrous K_2CO_3 (1eq.) were added and the reaction mixture was heated under reflux for 16hrs. The potassium salt was filtered off and the excess of ethanol was removed. The residue solidified on cooling to give desired product.

4.4 General procedure for the synthesis of compound.[12] 3 A Mixture of compound 2 (1eq.) was added in MeOH (100ml), potassium hydroxide (0.5eq) and heated with $CSCl_2$ (1eq.) and refluxed for about 12hrs at 65^{o}C. The separated solid was filtered, dried in vacuum and purified over a column of silica gel, eluted with C_6H_6: $CHCl_3$ (2:8 v/v) mixture to give a final product which was crystallized with $CHCl_3$.

4.5 General procedure for the synthesis of compound.[13,14] 4 To the solution of reactant 5 (1eq.) in absolute Methanol (60ml), methylchloroacetate (1eq.), hydrazine monohydrate and anhydrous K_2CO_3 (0.01mol) were added and the reaction mixture was heated under reflux for 16hrs. The potassium salt was filtered off and the excess of ethanol was removed. The residue solidified on cooling to give product.

4.6 General procedure for the synthesis of compound.[15] 5a-e Take the compound 4 and Aromatic aldehyde (listed in scheme 2) in a molar ratio (1:1 or 1:2) and make soluble in the EtOH (100ml) and reflux in for about 4-5hrs at 79C with a catalytic amount of glacial acetic acid (1-2 drops) on a water bath. The product 5a-e will be separated, recrystallized it from EtOH.

4.7 General procedure for the synthesis of compound.[16] 6a-e A mixture of compound 5 (0.15mmol) and $CuSO_4$ $5H_2O$ (0.05mmol) in toluene (0.5ml) was stirred magnetically and then heated for 0.55h at 110C reflux. Then, mercaptoacetic acids (0.15mmol) were added. The progress of the reaction was monitored by TLC using ethyl acetate/ petroleum ether (1/10-1/5). Upon completion of the reaction, the crude mixture was purified by column chromatography on silica gel (EtOAc/ ether) to afford the desired pure products 6a-e.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-benzylideneacetohydrazide (5a) Yield: 71.3 %; colorless solid, mp 172 – 174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.42 (s, 1H), 8.20 (d, *J* = 7.1.0 Hz, 2H), 8.12 (d, *J* = 7.5.0 Hz, 1H), 7.96 – 7.99 (m, 5H), 7.79-7.86 (m, 6H), 4.74 (s, 2H), 3.97 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 185.9, 173.3, 171.3, 159.2, 152.6, 150.4, 139.7, 130.6, 137.4, 129.3, 129.2, 128.9, 128.5, 128.2, 127.3, 117.8, 61.7, 56.5, ESIMS: m/z calculated for $C_{25}H_{19}N_7O_3S$ $(M+H)^+$ 498.53 found 497.12, Anal. Calc. for $C_{25}H_{19}N_7O_3S$: C, 60.35; H, 3.85; N, 19.71%; found: C, 60.31; H, 3.80; N, 19.69%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-methoxybenzylidene)acetohydrazide (5b) Yield: 58.2 %; colorless solid, mp 179 – 181 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.48 (s, 1H), 7.90 (d, *J* = 7.1.0 Hz, 2H), 8.12 (d, *J* = 7.5.0 Hz, 1H), 7.96 – 7.99 (m, 5H), 7.79-7.86 (m, 6H), 4.74 (s, 2H), 4.02 (s, 2H); 1.91 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 185.9, 173.3, 171.3, 159.2, 152.6, 150.4, 139.7, 130.6, 137.4, 129.3, 129.2, 128.9, 128.5, 128.2, 127.3, 117.8,114.1, 61.7,

56.5, 53.3 ESIMS: m/z calculated for $C_{26}H_{21}N_7O_4S$ $(M+H)^+$ 528.14 found 529.06 Anal. Calc. for $C_{26}H_{21}N_7O_4S$: C, 59.19; H, 4.01; N, 18.59; found: C, 59.22; H, 3.99; N, 18.56%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-methylbenzylidene)acetohydrazide (5c) Yield: 74.4 %; colorless solid, mp 180 – 182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.42 (s, 1H), 8.20 (d, *J* = 7.1.0 Hz, 2H), 8.12 (d, *J* = 7.5.0 Hz, 1H), 7.96 – 7.99 (m, 5H), 7.79-7.86 (m, 6H), 4.74 (s, 2H), 3.97 (s, 2H); 1.29 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 185.9, 173.3, 171.3, 159.2, 152.6, 150.4, 139.7, 130.6, 137.4, 129.3, 129.2, 128.9, 128.5, 128.2, 127.3, 117.8, 61.7, 56.5, 29.3 ESIMS: m/z calculated for $C_{26}H_{21}N_7O_3S$ $(M+H)^+$ 512.14 found 511.29 Anal. Calc. for $C_{26}H_{21}N_7O_3S$: C, 61.05; H, 4.14; N, 19.17%; found: C, 69.98; H, 4.11; N, 19.20%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(4-chlorobenzylidene)acetohydrazide (5d) Yield: 58.4 %; white solid, mp 179 – 180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.48 (s, 1H), 8.32-8.31 (d, *J* = 7.1.0 Hz, 2H), 8.01 (d, *J* = 7.5.0 Hz, 1H), 7.99 – 7.96 (m, 5H), 7.86-7.79 (m, 5H), 4.49 (s, 2H); 4.07 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 186.9, 173.3, 171.3, 159.2, 152.6, 150.4,140.0, 139.7, 137.6, 136.6, 130.2, 130.4, 133.2, 129.3, 129.2, 127.9, 128.5, 128.2, 127.3, 127.4, 118.0, 117.8, 53.8, 48.3. ESIMS: m/z calculated for $C_{25}H_{18}ClN_7O_3S$ $(M+H)^+$ 531.09 found 531.0 Anal. Calc. for $C_{25}H_{18}ClN_7O_3S$: C, 56.45; H, 3.41; N, 18.43%; found: C, 56.44; H, 3.41; N, 18.40%.

(E)-2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N'-(thiophen-2-ylmethylene)acetohydrazide (5e) Yield: 60.6 %; white solid, mp 182 – 183 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 10.47 (s, 1H), 8.70 (s, 1H), 8.33 (s, 1H), 8.12 (d, *J* = 7.5.0 Hz, 1H), 7.99 – 7.96 (m, 4H), 7.51-7.66 (m, 4H), 6.99 (m, 1H), 4.49 (s, 2H); 4.02 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 190.4, 173.1, 170.0, 155.2, 147.5, 143.2, 140.7, 138.0, 132.8, 130.4, 130.4, 130.4, 130, 128.7, 128.2, 128.2, 127.1, 126.2, 114.7, 61.6, 57.2 ESIMS: m/z calculated for $C_{27}H_{24}N_8O_3S$ $(M+H)^+$ 504.08 found 504.02.,Anal. Calc. for $C_{23}H_{17}N_7O_3S2$: C, 54.86; H, 3.40; N, 19.47; %found: C, 54.85; H, 43.39; N, 19.47%.

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide (6a) Yield: 62.2 %; white solid, mp 157 – 158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.37 (s, 1H), 8.39 (s, 1H), 8.02(d, j=7.5Hz,

1H), 7.77 – 7.69 (m, 3H), 7.51-7.41 (m, 3H), 7.27-7.33 (m, 5H), 5.90 (s, 1H), 4.64 (s, 2H), 3.89-3.72 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 190.4, 173.1, 170.0, 165.8, 157.2, 146.6, 138.7, 137.4, 133.7, 130.2, 130.2, 130.2, 129.6, 128.5, 128.5, 128.3, 128.3, 127.0, 125.9, 125.9, 114.7, 63.2, 57.3, 33.8.; ESIMS: m/z calculated for $C_{27}H_{21}N_7O_4S_2$ $(M+H)^+$ 572.11 found 572.10, Anal. Calc. for $C_{27}H_{21}N_7O_4S_2$: C, 56.73; H, 3.70; N, 17.15%; found: C, 56.72; H, 3.70; N, 17.14%.

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)acetamide (6b) Yield: 67.1 %; white solid, mp 134 – 135 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.37 (s, 1H), 8.39 (s, 1H), 8.02(d, j=7.5Hz, 1H), 7.87 – 7.69 (m, 5H), 7.51-7.41 (m, 3H), 6.84 (m, 2H), 5.90 (s, 1H), 4.64 (s, 2H), 3.88 (s, 2H), 3,82 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 190.5, 173.3, 169.1, 168.7, 157.0, 156.2, 144.4, 138.8, 137.9, 133.0, 131.2, 130.4, 130.4, 130.4, 129.2, 128.5, 128.5, 114.7, 113.9, 113.9, 63.3, 54.8, 33.7 ESIMS: m/z calculated for $C_{28}H_{23}N_7O_5S_2$ $(M+H)^+$ 602.12 found 602.1 Anal. Calc. $C_{28}H_{23}N_7O_5S_2$: C, 55.90; H, 3.85; N, 16.30%; found: C, 55.91; H, 3.85; N, 16.28%.

2-(5-((5-benzoyl-1H benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(4-oxo-2-(p-tolyl)thiazolidin-3-yl)acetamide (6c) Yield: 58.7 %; white solid, mp 155 – 156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm)) 11.37 (s, 1H), 8.39 (s, 1H), 8.02(d, j=7.5Hz, 1H), 7.87 – 7.80 (m, 3H), 7.51-7.41 (m, 3H), 7.33 (dd, j= 7.4Hz, 2H), 7.04 (dd, j=7.5, 2H), 5.90 (s, 1H), 4.64 (s, 2H), 3.88 (s, 2H), 3,82 (s, 2H), 2.7 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 190.6, 173.3, 169.1, 168.7, 157.1, 144.5, 138.8, 137.9, 133.7, 136.2, 132.7, 130.4, 130.4, 130.4, 128.5, 128.5, 128.4, 128.4, 114.7, 62.8, 54.9, 33.9, 21.7.; ESIMS: m/z calculated for $C_{28}H_{23}N_7O_4S_2$ $(M+H)^+$ 586.13 found 586.0 Anal. Calc. for $C_{28}H_{23}N_7O_4S_2$: C, 57.42; H, 3.96; N, 16.74%; found: C, 57.41; H, 3.95; N, 16.73%.

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)acetamide (6d) Yield: 55.4%; white solid, mp 160 – 162 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.37 (s, 1H), 8.39 (s, 1H), 8.02(d, j=7.5Hz, 1H), 7.87 – 7.80 (m, 3H), 7.51-7.41 (m, 3H), 7.33 (dd, j= 7.4Hz, 2H), 7.04 (dd, j=7.5, 2H), 5.90 (s, 1H), 4.64 (s, 2H), 3.88 (s, 2H), 3,82 (s, 2H).; ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 190.6, 173.3, 169.1, 168.7, 157.1, 144.5, 138.8, 137.9, 133.7, 136.2, 132.7, 130.4, 130.4, 130.4, 130.0, 130.0, 128.5, 128.4, 128.4, 128.4 114.7, 62.8, 54.9, 33.9,

ESIMS: m/z calculated for $C_{27}H_{20}ClN_7O_4S_2$ $(M+H)^+$ 606.07 found 605.07 Anal. Calc. for $C_{27}H_{20}ClN_7O_4S_2$: C, 53.51; H, 3.33; N, 16.18%; found: C, 53.50; H, 3.32; N, 16.18%.

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)-N-(4-oxo-2-(thiophen-2-yl)thiazolidin-3-yl)acetamide (6e) Yield: 71.1 %; white solid, mp 181 – 182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 11.37 (s, 1H), 8.39 (s, 1H), 8.02(d, j=7.5Hz, 1H), 7.87 – 7.80 (m, 3H), 7.51-7.41 (m, 3H), 7.30 (dd, j= 7.4Hz, 1H), 7.0 (t, j=7.5, 1H), 6.78 (d, j=7.0Hz, 1H) 5.90 (s, 1H), 4.64 (s, 2H), 3,82 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 190.6, 173.3, 169.1, 168.7, 157.1, 144.5, 138.8, 137.9, 133.7, 132.7, 130.4, 130.4, 130.4, 130.0, 129.0, 129.0, 128.5, 127.4, 126.7, 125.4 114.7, 62.8, 54.9, 33.9. ESIMS: m/z calculated for $C_{25}H_{19}N_7O_4S_3$ $(M+H)^+$ 578.07 found 578 Anal. Calc. for $C_{25}H_{19}N_7O_4S_3$: C, 51.98; H, 3.32; N, 16.97%; found: C, 51.97; H, 3.32; N, 16.95%.

CONCLUSION

In this present work, we have illustrated the primary attempts made approaching the perception of new potentially active compounds which were derived by straightforward and efficient procedure. Biology shows that substituted compounds lead to more active microbial activity. In future we are going to prepare more analogous of this compounds by introducing different substitutions to enhance the bioactivity.

Conflicts of interest

The author declares no conflicts of interest.

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