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Synthesis, Characterization and *in vitro* Antimicrobial Evaluation of Pyrazole Based Oxothiazolidine Hybrids

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ABSTRACT

In this work, pyrazole based oxothiazolidine hybrids, 4-{4-[2-(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-yl)-4-oxo-thiazolidin-3-yl]-phenyl}-morpholin-3-one (**11a-l**) were synthesized using molecular hybridization approach through Vilsmeier-Haack reaction. The titled compounds **11a-l** were characterized by using elemental analysis, IR, ^{1}H NMR and mass spectral studies. The antibacterial activity of **11a-l** was evaluated *in vitro* by agar cup plate method against *B. cocous*, *B. subtillis*, *E. coli* and *P. vulgaris*. The antifungal activity of compounds **11a-l** was evaluated *in vitro* by agar based disk diffusion method against *A. niger*. The results of antibacterial and antifungal evaluation were reported in terms of zone of inhibition measured in mm. The synthesized compounds **11a-l** exhibited moderate to good antibacterial and antifungal potential. Compound 4-{4-[2-(1-phenyl-3-(2-methoxy-phenyl)phenyl-1*H*-pyrazol-4-yl)-4-oxo-thiazolidin-3-yl]-phenyl}-morpholin-3-one (**11h**) emerged as a most potent antimicrobial agent displaying zone of inhibition 21, 20, 21, 24 and 20 mm against *B. cocous*, *B. subtillis*, *E. coli*, *P. vulgaris* and *A. niger*, respectively.

KEYWORDS

Pyrazole, Oxothiazolidine, Vilsmeier-Haack reaction, Antimicrobial Evaluation.

INTRODUCTION

The presence of the different substituents on the pyrazole ring, together with the change in the aromatic system such as thiazolidine may have an effect on *in vitro* antibacterial and antifungal activity of potential chemotherapeutics [1]. The transition metal complexes with thiazolidine ligands have been extensively used in last two decades as highly active catalyst, especially towards the polymerization of numerous and diverse olefins [2]. Some reports had explored the chemotherapeutics potential of thiazolidines [3]. Imines, products of the condensation of carbonyl compound and primary amines, are important molecules that have been extensively studied owing to their broad range of industrial and biomedical applications [4-6]. The relative ease of their preparation, as well as the facile modification of the electronic and steric factor of the ligands, together with their chelating properties toward different metals have made them attractive targets in the field of medicinal chemistry [7-10]. These are well documented with diversely

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pharmacological properties such as antibacterial [11], antifungal [12], antimalarial [13], anti-inflammatory [14] and antiviral [15]. Inspired by the aforementioned and continuing our work on Schiff base compounds and their applications, the pyrazole nucleus was incorporated into the design and architecture of the imine ligand, with the goal of finding compounds that elicit and enhance bioactivity.

In the present study, pyrazole-based oxothiazolidine hybrids were synthesized, characterized and evaluated them for antimicrobial activity. This study reports the synthesis of 4-{4-[2-(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]-phenyl}-morpholin-3-one (**11a-l**) and their antimicrobial activity against fungi, Gram-positive and Gram-negative bacteria.

EXPERIMENTAL

The chemicals and solvents used in the synthesis were of analytical grade and procured from Rankem Pvt. Ltd. India. The melting point of synthesised compounds was determined by using open capillary method and are reported uncorrected. FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan) was used for IR spectral characterization, using DRS probe KBr pellet. The Bruker-Avance II-400 MHz instrument was used for proton NMR spectra by using DMSO-d_6 as solvent. The mass spectrum was obtained by using GCMS-QP-2010 spectrometer. Chemicals procured from Merck Chemicals, India and used for biological activity included peptone and beef extract (microbiology grade), agar (bacteriological grade), sodium chloride and distilled water (Emplura double distilled water).

Synthesis of 2-Phenylamino-ethanol (2): Aniline (0.01 mole) was added in round bottom flask, stirred well and ethylene oxide gas was passed through it. Reaction progress was continuously monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled and poured on ice water. The solid material, compound **2** was filtered and purified by recrystallization.

Synthesis of 4-phenyl-morpholin-3-one (3): Chloroacetyl chloride was added dropwise manner in a previously cooled round bottom flask containing compound **2** (0.01 mol), DMF and K_2CO_3 (0.02 mol) and maintained the temperature at 0 ºC. After completion of the addition, heated the reaction mixture to 60 ºC for 4 h. The solid material, compound **3** was filtered and purified by recrystallization from ethanol. The progress and completion of the reaction was monitored by TLC.

Synthesis of 4-(4-nitrophenyl)morpholin-3-one (4): In a 250 mL round bottom flask, conc. H_2SO_4 (0.03 mol) was added and cooled to 0 ºC. To this, conc. HNO_3 (0.03 mol) was added dropwise. In this nitrating mixture, compound **3** (0.01 mol) was added in portion. After completion of the addition, reaction mixture was stirred at 60 ºC for 3 h. The reaction mixture was cooled and poured on ice water. The solid material, compound **4** was filtered and purified by recrystallization from ethanol.

Synthesis of 4-(4-aminophenyl)morpholin-3-one (5): In a 250 mL round bottom flask, hydrochloric acid (3 parts) was taken and cooled to 5 ºC. To this, tin (Sn) metal was added. In this reaction mixture, compound **4** (0.01 mol) was added and heat the reaction mixture at 70 ºC for 5 h. After completion of reaction, the reaction mixture was cooled and poured on ice water. Neutralized the mixture with NaOH solution, extract with ethyl acetate and evaporate the ethyl acetate fraction to yield compound **5**.

Synthesis of *N*-Phenyl-*N*'-(1-(substituted)phenyl ethylidene)hydrazine (8a-l): A mixture of phenyl hydrazine (**6**, 1.08 g) and substituted acetophenone (**7a**, 1.2 g) in absolute ethanol was refluxed on water bath for 4 h in the catalytic presence of 1 mL glacial acetic acid. After the completion of reaction, the reaction mixture was allowed to cool. Compound **8** was crystallized and purified by recrystallization.

Synthesis of 1-phenyl-3-(substituted)phenyl-1*H*-pyrazole-4-carbaldehyde (9a-l): *N*-Phenyl-*N*′-(1-(substituted)phenylethylidene)hydrazine (**8a**, 0.84 g) was added in a mixture of Vilsmeier-Haack reagent (prepared by dropwise addition of 1.2 mL $POCl_3$ in ice-cooled 10 mL DMF) and refluxed for 6 h. The reaction mixture was poured on crushed ice followed by neutralization using sodium bicarbonate. The crude product was isolated and crystallized from methanol.

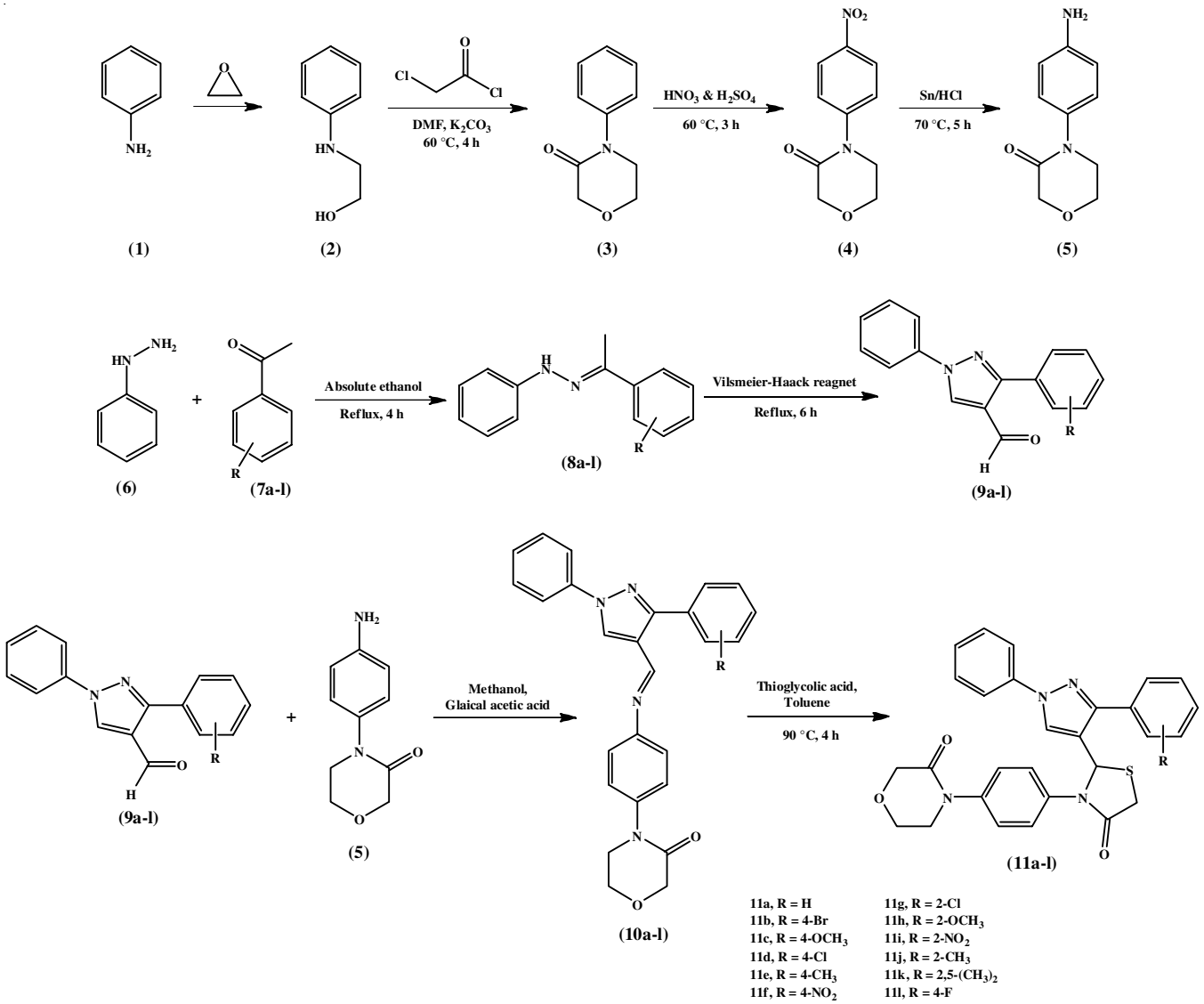
Synthesis of 4-{4-[(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-ylmethylene)amino]phenyl}morpholin-3-one (10a-l): Substituted 1,3-diphenyl-1*H*-pyrazol-4-carbaldehyde (**9**, 0.80 mmol) was added in 20-25 mL methanol with catalytic amount of glacial acetic acid. In this mixture, 4-(4-aminophenyl)morpholin-3-one (**5**, 0.80 mmol) was added, stirred the resulting solution at room temperature for 2 h. The solid product was filtered, washed with cool methanol and recrystallized from methanol to yield compound **10a-l**.

Synthesis of 4-{4-[2-(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11a-l): To a stirred solution of compound **10a-l** (0.47 mmol) and toluene at room temperature, thioglycolic acid (0.52 mmol) was added. Heated the resultant mixture at 90 ºC for 4 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The solid sticky material was treated with sodium bicarbonate solution until the reaction mass become basic. The product was separated out, filtered, washed with distilled water and recrystallized from methanol to yield compound **11a-l.** The TLC system used was MDC:MeOH (9:1) (**Scheme-I**).

Spectral data

4-{4-[2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11a): White solid; yield: 81%; R_f value: 0.46 (ethyl acetate:hexane, 8:2); m.p.: 166 ºC; IR (KBr, ν_{max}, cm^{-1}): 3206.22 (C-H *str*. in arom.), 2850.75 (C-H *str*. in alkane), 1625.49 (C=O *str*. in amide), 835.98 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.12-7.98 (multiplet, 15H, aromatic), 4.29 (singlet, 2H of $–CH_2$), 3.90-4.00 (triplet, 2H of $–CH_2$), 3.06-3.08 (triplet, 2H of $–CH_2$), 1.15 (singlet, 1H of –CH), 3.86 (singlet, 2H of $–CH_2$); MS (*m/z*): 496 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{24}N_4O_3S$; C: 67.72 (66.92); H: 4.87 (3.97); N: 11.28 (10.72); O: 9.67 (9.05); S: 6.46 (5.73).

4-{4-[2-(1-Phenyl-3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11b): Orange solid; yield: 85%; R_f value: 0.39 (ethyl acetate:hexane, 8:2); m.p.: 172 ºC; IR (KBr, ν_{max}, cm^{-1}): 3269.93 (C-H *str*. in arom.), 2773.39 (C-H *str*. in alkane), 1599.70 (C=O *str*. in amide), 830.51 (*p*-disub. arom.), 773.18 (-C-Br); ^{1}H NMR (DMSO-d_6) in δ



Scheme-I: Synthetic scheme of 4-{4-[2-(1-phenyl-3-(substituted)phenyl-1*H*- pyrazol-4-yl)-4-oxothiazolidin-3-yl]-phenyl}morpholin-3-one (**11a-l**)

ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.29 (singlet, 2H of $-CH_2$), 4.29 (singlet, 2H of $-CH_2$), 3.66-3.69 (triplet, 2H of $-CH_2$), 3.96-3.99 (triplet, 2H of $-CH_2$), 3.87 (singlet, 1H of –CH); MS (*m/z*): 575 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{23}N_4O_3SBr$; C: 58.44 (57.85); H: 4.03 (3.80); Br: 13.88 (13.02); N: 9.74 (8.98); O: 8.34 (7.90); S: 5.57 (4.79).

4-{4-[2-(1-Phenyl-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11c): Off white solid; yield: 79%; R_f value: 0.42 (ethyl acetate:hexane, 8:2); m.p.: 164 ºC; IR (KBr, ν_{max}, cm^{-1}): 3270.50 (C-H *str*. in arom.), 2751.18 (C-H *str.* in alkane), 1580.52 (C=O *str.* in amide), 810.12 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.05-7.84 (multiplet, 14H, aromatic), 6.80 (singlet, 2H of $-CH_2$), 4.15 (singlet, 2H of $-CH_2$), 3.25-3.28 (triplet, 2H of $-CH_2$), 3.84-3.88 (triplet, 2H of $-CH_2$), 3.93 (singlet, 1H of –CH), 2.71 (singlet, 3H of $-CH_3$); MS (*m/z*): 526 (M^+); Elemental anal. calcd. (found) % for $C_{29}H_{26}N_4O_4S$; C: 66.14 (65.64); H: 4.98 (4.15); N: 10.64 (9.98); O: 12.15 (11.71); S: 6.09 (5.80).

4-{4-[2-(1-Phenyl-3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11d): White solid; yield: 74%; R_f value: 0.38 (ethyl acetate:hexane, 8:2); m.p.: 169 ºC; IR (KBr, ν_{max}, cm^{-1}): 3238.12 (C-H *str*. in arom.), 2773.39 (C-H *str*. in alkane), 1599.70 (C=O *str*. in amide), 860.69 (*p*-disub. arom.), 720 (-C-Cl); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.02-7.90 (multiplet, 14H, aromatic), 6.40 (singlet, 2H of $-CH_2$), 4.62 (singlet, 2H of $-CH_2$), 3.54-3.58 (triplet, 2H of $-CH_2$), 3.90-3.93 (triplet, 2H of $-CH_2$), 3.82 (singlet, 1H of –CH); MS (*m/z*): 531 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{23}ClN_4O_3S$; C: 63.33 (62.99); H: 4.37 (4.01); Cl: 6.68 (5.89); N: 10.55 (10.12); O: 9.04 (8.80); S: 6.04 (5.68).

4-{4-[2-(1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11e): Off white solid; yield: 82%; R_f value: 0.44 (ethyl acetate:hexane, 8:2); m.p.: 178 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240.71 (C-H *str*. in arom.), 2749.51 (C-H *str*. in alkane), 1546.19 (C=O *str*. in amide), 848.94 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.08-7.90 (multiplet, 14H, aromatic), 6.40 (singlet, 2H of $-CH_2$), 4.58 (singlet, 2H of $-CH_2$), 3.56-3.59 (triplet, 2H of $-CH_2$), 3.84-3.87 (triplet, 2H of $-CH_2$), 3.81 (singlet, 1H of –CH), 1.01 (singlet, 3H of $-CH_3$); MS (*m/z*): 510 (M^+); Elemental

anal. calcd. (found) % for $C_{29}H_{26}N_4O_3S$; C: 68.21 (67.67); H: 5.13 (4.81); N: 10.97 (9.99); O: 9.40 (8.89); S: 6.28 (5.98).

4-{4-[2-(1-Phenyl-3-(4-nitrophenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11f): Yellow solid; yield: 75%; R_f value: 0.48 (ethyl acetate:hexane, 8:2); m.p.: 184 ºC; IR (KBr, ν_{max}, cm^{-1}): 3220.11 (C-H *str*. in arom.), 2790.26 (C-H str. in alkane), 1510.20 (C=O *str*. in amide), 1470 (-NO_2 *str.*), 818.12 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.19 (singlet, 2H of –CH_2), 4.41 (singlet, 2H of –CH_2), 3.51-3.54 (triplet, 2H of –CH_2), 3.96-3.99 (triplet, 2H of –CH_2), 3.87 (singlet, 1H of –CH); MS (*m/z*): 541 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{23}N_5O_5S$; C: 62.10 (61.39); H: 4.28 (3.77); N: 12.93 (12.15); O: 14.77 (13.14); S: 5.92 (4.98).

4-{4-[2-(1-Phenyl-3-(2-chlorophenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11g): White solid; yield: 78%; R_f value: 0.39 (ethyl acetate:hexane, 8:2); m.p.: 168 ºC; IR (KBr, ν_{max}, cm^{-1}): 3280.25 (C-H *str*. in arom.), 2652.14 (C-H *str*. in alkane), 1530.22 (C=O *str*. in amide), 852.18 (*p*-disub. arom.), 721 (-C-Cl); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.18 (singlet, 2H of –CH_2), 4.52 (singlet, 2H of –CH_2), 3.86-3.89 (triplet, 2H of –CH_2), 3.96-3.99 (triplet, 2H of –CH_2), 3.92 (singlet, 1H of –CH); MS (*m/z*): 531 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{23}N_4O_3SCl$; C: 63.33 (62.14); H: 4.37 (3.85); Cl: 6.68 (6.12); N: 10.55 (10.10); O: 9.04 (8.45); S: 6.04 (5.72).

4-{4-[2-(1-Phenyl-3-(2-methoxyphenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11h): Off white solid; yield: 80%; R_f value: 0.41 (ethyl acetate: hexane, 8:2); m.p.: 162 ºC; IR (KBr, ν_{max}, cm^{-1}): 3210.42 (C-H *str*. in arom.), 2710.41 (C-H *str*. in alkane), 1542.29 (C=O *str*. in amide), 851.72 (*p*-disub. arom.), 773.18 (-C-Br); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.05-7.95 (multiplet, 14H, aromatic), 6.32 (singlet, 2H of –CH_2), 4.39 (singlet, 2H of –CH_2), 3.46-3.49 (triplet, 2H of –CH_2), 3.86-3.89 (triplet, 2H of –CH_2), 3.81 (singlet, 1H of –CH), 2.60 (singlet, 3H of -CH_3); MS (*m/z*): 526 (M^+); Elemental anal. calcd. (found) % for $C_{29}H_{26}N_4O_4S$; C: 66.14 (65.64); H: 4.98 (4.52); N: 10.64 (10.71); O: 12.15 (11.82); S: 6.09 (5.19).

4-{4-[2-(1-Phenyl-3-(2-nitrophenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11i): Yellow solid; yield: 82%; R_f value: 0.42 (ethyl acetate:hexane, 8:2); m.p.: 186 ºC; IR (KBr, ν_{max}, cm^{-1}): 3288.11 (C-H *str*. in arom.), 2711.86 (C-H *str*. in alkane), 1530.68 (C=O *str*. in amide), 1511 (-NO_2 *str.*), 860.12 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.32 (singlet, 2H of –CH_2), 4.33 (singlet, 2H of –CH_2), 3.69-3.72 (triplet, 2H of –CH_2), 3.96-3.99 (triplet, 2H of –CH_2), 3.91 (singlet, 1H of –CH); MS (m/z): 541 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{23}N_5O_5S$; C: 62.10 (61.51); H: 4.28 (4.01); N: 12.93 (11.20); O: 14.77 (14.14); S: 5.92 (5.28).

4-{4-[2-(1-Phenyl-3-(*o*-tolyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11j): White solid; yield: 86%; R_f value: 0.47 (ethyl acetate:hexane, 8:2); m.p.: 180 ºC; IR (KBr, ν_{max}, cm^{-1}): 3225.44 (C-H *str*. in arom.), 2710.13 (C-H *str*. in alkane), 1576.19 (C=O *str*. in amide), 860.89 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.31 (singlet, 2H of –CH_2), 4.22 (singlet, 2H of –CH_2), 3.61-3.65 (triplet, 2H of –CH_2), 3.96-3.99 (triplet, 2H of –CH_2), 3.81 (singlet, 1H of –CH), 0.6 (singlet, 3H of –CH_3); MS (*m/z*): 510 (M^+); Elemental anal. calcd. (found) % for $C_{29}H_{26}N_4O_3S$; C: 68.21 (67.69); H: 5.13 (4.78); N: 10.97 (9.84); O: 9.40 (8.78); S: 6.28 (5.46).

4-{4-[2-(1-Phenyl-3-(2,5-dimethylphenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]-phenyl}-morpholin-3-one (11k): White solid; yield: 70%; R_f value: 0.35 (ethyl acetate: hexane, 8:2); m.p.: 167 ºC; IR (KBr, ν_{max}, cm^{-1}): 3198.74 (C-H *str*. in arom.), 2812.39 (C-H *str*. in alkane), 1610.19 (C=O *str*. in amide), 841.23 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.37 (singlet, 2H of –CH_2), 4.15 (singlet, 2H of –CH_2), 3.41-3.44 (triplet, 2H of –CH_2), 3.91-3.94 (triplet, 2H of –CH_2), 3.75 (singlet, 1H of –CH), 1.1 (singlet, 6H of –CH_3); MS (*m/z*): 524 (M^+); Elemental anal. calcd. (found) % for $C_{30}H_{28}N_4O_3S$; C: 68.68 (67.98); H: 5.38 (4.71); N: 10.68 (9.28); O: 9.15 (8.53); S: 6.11 (5.92).

4-{4-[2-(1-Phenyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (11l): White solid; yield: 77%; R_f value: 0.43 (ethyl acetate:hexane, 8:2); m.p.: 202 ºC; IR (KBr, ν_{max}, cm^{-1}): 3220.12 (C-H *str*. in arom.), 2718.42 (C-H *str*. in alkane), 1573.29 (C=O *str*. in amide), 1100 (-C-F), 828.75 (*p*-disub. arom.); ^{1}H NMR (DMSO-d_6) in δ ppm: 7.10-7.97 (multiplet, 14H, aromatic), 6.35 (singlet, 2H of –CH_2), 4.40 (singlet, 2H of –CH_2), 3.51-3.54 (triplet, 2H of –CH_2), 3.84-3.89 (triplet, 2H of –CH_2), 3.81 (singlet, 1H of –CH); MS (*m/z*): 514 (M^+); Elemental anal. calcd. (found) % for $C_{28}H_{23}N_4O_3SF$; C: 65.36 (64.54); H: 4.51 (3.62); F: 3.69 (2.88); N: 10.89 (9.68); O: 9.33 (8.80); S: 6.23 (5.71).

Biological activity

Antibacterial activity: Agar cup plate method [16] was used for antibacterial evaluation of titled compounds **11a-l**. The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method was inoculated aseptically for 24 h. Subcultures of *B. cocous*, *B. subtillis*, *E. coli* and *P. vulgaris* were prepared in separate conical flasks at 40-50 ºC. About 25 mL content of the flask were poured and evenly spread in a petridish (13 cm in diameter) and allowed to set for 2 h. The cup (10 mm in diameter) were formed with the help of borar in agar medium and filled with 0.04 mL (40 mg) solution of sample in DMF. The plates were incubated at 37 ºC for 24 h and the control was also maintained with 0.04 mL of DMF. The difference of zone of inhibition of the bacterial growth with control was measured in mm. Several drugs *viz*. amoxicillin, benzoyl penicillin, ciprofloxacin and erythromycin were used as standard drugs.

Antifungal activity: Antifungal activity of the titled compounds **11a-l** was evaluated by agar based disk-diffusion method [17] against fungal strains *A. niger*. The culture was maintained on Sabouraud's agar slants. Sterilized Sabouraud′s agar medium was inoculated with 72 h. The 0.5 mL of suspension of fungal spores was used to prepare subculture. About 25 mL of the inoculated medium was evenly spread in a petri-dish and allowed to set for 2 h. The cups (10 mm in diameter) were punched. The plates were incubated at 30 ºC for 48 h. After the completion of incubation period, the zones of inhibition of growth in the form of diameter (in mm) was measured along the test solution,

in each petri-dish one cup was filled up with solvent, which acts as control. The standard drug used was Griseofulvin.

RESULTS AND DISCUSSION

The synthetic route of titled compounds **11a-l** is outlined in **Scheme-I**. Aniline was used as starting material and reacted with ethylene oxide gas for the synthesis of 2-phenylamino-ethanol (**2**). Compound **2** was then reacted with chloroacetyl chloride to synthesize 4-phenyl-morpholin-3-one (**3**). Compound **3** was further treated with nitrating mixture and converted to 4-(4-nitrophenyl)morpholin-3-one (**4**). Compound **4** was then reduced with tin to yield 4-(4-aminophenyl)morpholin-3-one (**5**). The phenyl hydrazine (**6**) was reacted with substituted acetophenones **7a-l** to give respective imines, *N*-Phenyl-*N*′-(1-(substituted)phenyl-ethylidene)hydrazine (**8a-l**), which *via* Vilsmeier-Haack reaction was converted to substituted pyrazole derivatives, 1-phenyl-3-(substituted)phenyl-1*H*-pyrazole-4-carbaldehyde (**9a-l**). Compound **9a-l** was finally reacted with compound **5** to yield 4-{4-[(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-ylmethylene)amino]phenyl}morpholin-3-one (**10a-l**), which on reaction with thioglycolic acid give titled compounds 4-{4-[2-(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (**11a-l**). The purity of the synthesized compounds was ascertained by TLC. The structures of the titled compounds **11a-l** were confirmed by elemental analysis and spectral analysis data.

Antibacterial activity: Antibacterial activity of compounds **11a-l** was evaluated against Gram-positive *B. cocous* & *B. subtillis* and Gram-negative bacteria *Proteus vulgaris* & *E. coli* by agar cup plate method. The results of comparative antibacterial activity of titled compounds **11a-l** against studied bacteria are shown in Fig. 1. It was observed that synthesized compounds **11a-l** exhibited moderate to good antibacterial potential (Table-1). Among the synthesized series of compounds **11a-l**, 4-{4-[2-(1-phenyl-3-(2-methoxyphenyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (**11h**) emerged as a most potent antibacterial agent displaying zone of inhibition 21, 20, 21 and 24 mm against *B. cocous*, *B. subtillis*, *E. coli* and *P. vulgaris*, respectively.

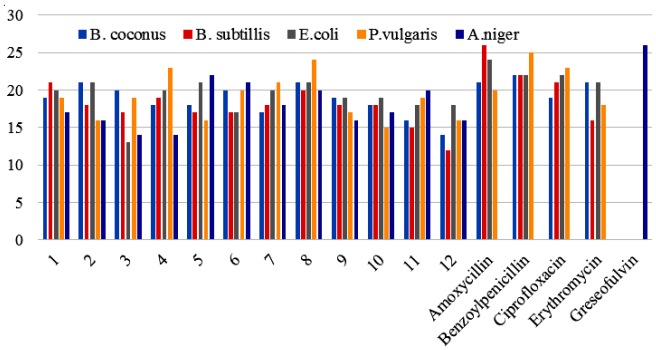


Fig. 1. Graphical representation of antibacterial and antifungal activities of titled compounds **11a-l**

Antifungal activity: Antifungal activity of compounds **11a-l** was evaluated against *A. niger* by agar based disk-diffusion method. The results of comparative antifungal activity of titled compounds **11a-l** against *A. niger* is shown in Table-1. It was observed that compounds **11a-l** exhibited moderate to good antifungal activity. Among the synthesized series of compounds **11a-l**, 4-{4-[2-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}morpholin-3-one (**11e**) exhibited highest activity against fungal strain *A. niger*.

Conclusion

The results obtained in this study revealed that pyrazole based oxothiazolidine hybrids, 4-{4-[2-(1-phenyl-3-(substituted)phenyl-1*H*-pyrazol-4-yl)-4-oxothiazolidin-3-yl]phenyl}-morpholin-3-one (**11a-l**) exhibited a significant antibacterial and antifungal activities, thus can be further explored as a lead in the development of newer antimicrobial agents and may play a vital role in the development of newer chemotherapeutic agents.

TABLE-1
ANTIMICROBIAL ACTIVITY OF 4-{4-[2-(1-PHENYL-3-(SUBSTITUTED)PHENYL-1*H*-PYRAZOL-4-YL)-4-OXO-THIAZOLIDIN-3-YL]-PHENYL}-MORPHOLIN-3-ONE (**11a-l**)

Compound at concentration of 40 µg/mL	Zone of inhibition (mm)				
	Antibacterial activity				Antifungal activity
	Gram-positive		Gram-negative		
	B. cocous	*B. subtillis*	*E. coli*	*P. vulgaris*	*A. niger*
11a	19	21	20	19	17
11b	21	18	21	16	16
11c	20	17	13	19	14
11d	18	19	20	23	14
11e	18	17	21	16	22
11f	20	17	17	20	21
11g	17	18	20	21	18
11h	21	20	21	24	20
11i	19	18	19	17	16
11j	18	18	19	15	17
11k	16	15	18	19	20
11l	14	12	18	16	16
Amoxycillin	21	26	24	20	–
Benzoylpenicillin	22	22	22	25	–
Ciprofloxacin	19	21	22	23	–
Erythromycin	21	16	21	18	–
Griseofulvin	–	–	–	–	26

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