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Study of biophysical properties, synthesis and biological evaluations of new thiazolidine-2,4-dione conjugates

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Thiazolidine-2,4-dione and its derivatives are acting as antimicrobial and antitubercular agents. Computational approach 2D-QSAR is used for prediction of antitubercular activity of the synthetic derivatives. 2D-QSAR generated model using PLSR method which predicted the statistically significant r^2 = 0.3333, q^2= 0.4000, pred_r^2 = -1.9753 and F test = 3.0000. 2D-QSAR generated equation of pMICs is denoted the antitubercular activity correlated with thermodynamic descriptor T_2_2_O. Pharmacokinetic properties absorption, distribution, metabolism, excretion are also predicted which are useful for design the derivatives. A designed derivatives of (*Z*)-2-(5-substituted-2,4-dioxothiazolidin-3-yl)-*N*-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide **(C_1-C_{10})** are synthesized and spectrally characterized using IR, ^{1}H NMR, ^{13}C NMR and mass spectral data analysis as well as biologically evaluated against antitubercular and antimicrobial activities. From the biologically evaluated derivatives, compounds C_1 and C_4 were found to be active against the different antimicrobial species. Compounds C_7 and C_{10} are more progressive than others against antitubercular species.

Keywords: 2D-QSAR, PLSR method, T_2_2_O, ADME Properties, Antimicrobial activity, Antitubercular activity

The treatment of infectious diseases still remains an important and challenging problem because of a combination factors, including emerging infectious diseases and increasing number of multi-drug resistant microbial pathogens with particular relevance for antimicrobial species[1,2,3]. So, the research to obtain a new antibacterial compounds is vitally important. Thiazolidine-2,4-dione having heterocyclic ring system and both nitrogen and sulfur atoms are of a great importance and receiving special attention with proven utility as antimicrobial and antitubercular resistance in medicinal chemistry. Thiazolidine-2,4-dione derivatives are studied extensively and found to having diverse chemical reactivity[4,5]. Thiazolidine-2,4-dione derivatives are displayed a broad spectrum of biological activities including antimicrobial[6,7], antidiabetic[8,9], antiobesity[10], anti-inflammatory[11], antioxidant[12] etc. Triazine cotains three carbon nitrogen double bond in its structure. Triazine contains three isomers from which 1,3,5-triazine owing to a wide range of biological applications, such as antimicrobial[13], anticancer[14], anti-tubercular[15], antitumor[16] and antiinflammatory[17]. In addition to this CH_3 and OCH_3 groups it contains 1,3,5-triazine which have electron withdrawing group that increase the biological activity.

In vitro, *in vivo* or *in silico* methods are being used in early stages of drug development to avoid possible failures, especially those related with drug metabolism, pharmacokinetic profiles and toxicity issues[18]. So, we studied the structure activity relationship for antitubercular activity and absorption, distribution, metabolism, excretion (ADME) properties. Quantitative structure activity relationship (QSAR) is a useful tool which maximizes the potential of identifying new lead moieties. In the lead optimization phase of the synthetic project various QSAR procedures with the aid of computer technology are proposed. The interactions of drugs with their biological counterparts are determined by intermolecular forces, i.e. by hydrophobic, polar, electrostatic, and steric interactions[19,20]. The success of QSAR approach can be explained by the insight offered into the structural determination of chemical properties and the possibility to estimate the properties of new chemical moiety. 2D-QSAR prediction was carried out by PLSR method on VLifeMDS software and predicted pMICs were compared with actual pMICs.Swiss ADME tool is used for prediction of ADME properties. Because of pharmaceutical advantages of 2,4-thiazolidinedione

we had decided to synthesized derivatives of 2,4-thiazolidinedione. Synthetic compounds were spectrally evicted for IR, ^{1}H NMR, ^{13}C NMR and Mass data and biologically evicted for antimicrobial and antitubercular activity.

Experimental Section

General materials

Analytical grade chemicals were used for the synthesis and purification. Melting points were measured on a Fisher-Johns melting point instrument. Completion of the reaction was checked out by TLC on silica gel plate which was visualized by applying UV-light and iodine chamber. FTIR spectra were recorded by model FTIR 8400S and frequency measured in cm^{-1} unit. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz on Bruker Avance II spectrometer instruments in DMSO-d_6 and $CDCl_3$. Chemical shifts were investigated in parts per million downfield from tetramethylsilane. Mass spectra were investigated on LC-MS. Structures and nomenclatures of the compounds were created on Perkin Elmer ChemBioOffice Ultra 14.0.0.117 software. 2D-QSAR carried out from VLifeMDS software. SwissADME online tool is used for prediction of ADME properties.

General procedure for synthesis of (E)-5-substitutidenethiazolidine-2,4-dione) (A_1-A_{10})

The substituted aldehydes (0.01 mol), 2,4-thiazolidinedione (0.01 mol), piperidine (0.01 mol) and acetic acid (0.01 mol) were dissolved in toluene (25 mL) and heated up to refluxed for azeotropic removal of water around 16 h. The mixture was cool up to 5°C, precipitates obtained filter it, washed with distilled water and recrystallized from appropriate solvents to obtain pure products (A_1-A_{10}). Physical data of compounds A_1-A_{10} are given in Table 1.

General procedure for synthesis of 2-chloro-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)phenyl)-acetamide (B)

The compound 4-methoxy-6-methyl-1,3,5-triazin-2-amine (0.10 mol) was dissolved in dichloromethane (20 mL) which followed by drop wise addition of chloroacetyl chloride (0.15 mol) and TEA (0.10 mol) which stirred around 3 h maintaining 0°C. The reaction progress was monitored by TLC using solvent toluene:methanol:ethyl acetate (2:3:5). After the completion of the reaction, the reaction mass was fallout in water and formed organic layer was separated out. The separated liquid compound was dried, washed and recrystallized with methanol to get a pure product (B). %Yield = 67, m.p. = 114°C, M. F. = $C_7H_9O_2N_4Cl$.

General procedure for synthesis of (Z)-2-(5-ethylidene-2,4-dioxothiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamid (C_1-C_{10})

The compounds (A) (0.01 mol) and (B) (0.01 mol) were dissolved in ethanol (10 mL) and added K_2CO_3 (0.01 mol). The reaction mixtures were refluxed up to 80°C for 4 h. The progresses of the reaction were monitored by TLC using toluene:ethyl acetate (2.5:7.5), after every 30 min. After completion of the reaction, the mixture was cooled, diluted with water and filtered it. The separated solid compounds were washed, dried and recrystallized with methanol to obtain compounds (C_1-C_{10}). Physical data of compounds C_1-C_{10} are given in Table 2.

Spectral data of compounds

(Z)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (A_3)

IR (KBr) ν cm^{-1}: 3238 (N-H stretching), 3104 (C-H stretching, aromatic), 2853 (C-H stretching, C=CH), 1726, 1665 (C=O stretching), 1614 (C=C stretching), 1545 (C=C stretching, C=CH), 1342 (C-N stretching),

Table 1 — Physical data of compounds (A_1-A_{10})

Code	R	% Yield	M.P. (°C)	M.F.
A_1	4-Nitrobenzaldehyde	58	272	$C_{10}H_6N_2O_4S$
A_2	4-Pyridinecarboxaldehyde	65	245	$C_9H_5N_2O_2S$
A_3	Furfuraldehyde	71	225	$C_8H_4NO_3S$
A_4	4-Methyoxybenzaldehyde	59	230	$C_{11}H_9NO_3S$
A_5	2-Pyridinecarboxaldehyde	63	252	$C_9H_5N_2O_2S$
A_6	4-Chlorobenzaldehyde	64	240	$C_{10}H_6NO_2SCl$
A_7	4-Methylbenzaldehyde	62	210	$C_{11}H_9NO_2S$
A_8	4-Propylbenzaldehyde	56	217	$C_{13}H_{13}NO_2S$
A_9	Cinnamaldehyde	59	222	$C_{12}H_8NO_2S$
A_{10}	4-(diethylamino)salisaldehyde	64	277	$C_{14}H_{16}N_2O_3S$

Table 2 — Physical data of compounds (C_1-C_{10})

Code	R	% Yield	M.P. (°C)	M.F.
C_1	4-Nitrobenzaldehyde	60	135	$C_{18}H_{15}O_7N_5S$
C_2	4-Pyridinecarboxaldehyde	67	144	$C_{17}H_{15}O_5N_5S$
C_3	Furfuraldehyde	63	149	$C_{16}H_{14}O_6N_4S$
C_4	4-Methyoxybenzaldehyde	69	158	$C_{19}H_{18}O_6N_4S$
C_5	2-Pyridinecarboxaldehyde	73	138	$C_{17}H_{15}O_5N_4S$
C_6	4-Chlorobenzaldehyde	65	153	$C_{18}H_{15}O_5N_4SCl$
C_7	4-Methylbenzaldehyde	63	148	$C_{19}H_{18}O_5N_4S$
C_8	P-Propylbenzaldehyde	66	145	$C_{21}H_{22}O_5N_4S$
C_9	Cinnamaldehyde	68	157	$C_{20}H_{18}O_5N_4S$
C_{10}	4-(diethylamino)salisaldehyde	67	136	$C_{22}H_{25}O_5N_5S$

1268 (C-H bending), 932 (C-H out of plane, aromatic),756 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.31 (s, 1H, TZD N-H), 7.88(d, 1H, *J*=2.76 Hz, furan), 7.54 (s, 1H, C=CH), 6.95 (d, 1H, *J* = 3.48 Hz, furan), 6.63 (t, 1H, *J* = 2.16 Hz, furan).

(Z)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione (A_7)

IR (KBr) *v* cm^{-1}: 3202 (N-H stretching), 3119 (C-H stretching, aromatic), 3050 (C-H stretching, C=CH), 2850 (C-H stretching, OCH_3), 1753, 1679 (C=O stretching), 1609 (C=C stretching, aromatic), 1538 (C=C stretching, C=CH), 1348 (C-H bending, OCH_3), 1285 (C-H bending, C=CH), 1153 (C-N stretching), 1008 (C-O stretching), 950 (C-H out of plane, aromatic), 761 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.27 (s, 1H, TZD N-H), 8.95 (d, 2H, *J* = 6.77 Hz, 4-methoxyphenyl), 8.21 (d, 2H, *J* = 5.43 Hz, 4-methoxyphenyl), 7.73 (s, 1H, C=CH).

(E)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-2-(5-(4-nitrobenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide C_1

IR (KBr) *v* cm^{-1}: 3316 (N-H stretching), 3180 (C-H stretching, aromatic), 3076, 2969, 2915 (C-H stretching, aliphatic), 2869 (C-H stretching, C=CH), 1714, 1667 (C=O stretching), 1598 (C=C stretching, aromatic), 1496 (C-H bending, CH_3), 1348 (C-H bending, CH_2), 1293 (C-N stretching), 1192 (C-O-C stretching), 1087 (C-H bending, aromatic), 723 (C-S stretching);^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.43 (s, 1H, TZD N-H), 8.95 (d, 2H, *J* = 6.48 Hz, 4-nitrophenyl),8.03 (s, 1H, C=CH), 7.59 (d, 2H, *J* = 2.52 Hz,4-nitrophenyl),4.92 (s, 2H, N-$\underline{CH_2}$-CO), 4.55 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 179.72 (C_3, 1,3,5-triazin), 174.29 (C_2 TZD), 170.51 (C_3, 1,3,5-triazin), 166.74 (N-CH_2-$\underline{C}$O-NH), 162.46 (C_4, TZD), 151.97 (C_1, 1,3,5-triazin), 143.20 (C=$\underline{C}$H), 139.82, 133.41, 130.06, 128.94, 116.72, (aromatic carbons), 55.78 (OCH_3), 49.38 (N-$\underline{C}H_2$-CO), 22.18 (CH_3); LC-MS (m/z): 445 M^+, 447 $[M+2]^+$.

(E)-2-(2,4-dioxo-5-(pyridin-4-ylmethylene) thiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triaz in-2-yl)acetamide C_2

IR (KBr) *v* cm^{-1}: 3334 (N-H stretching), 3187 (C-H stretching, aromatic), 3083, 2978, 2927 (C-H stretching, aliphatic), 2863 (C-H stretching, C=CH), 1719, 1657(C=O stretching), 1604 (C=C stretching, aromatic), 1528 (C=N stretching, aromatic), 1493 (C-H bending, CH_3), 1356 (C-H bending, CH_2), 1278 (C-N stretching), 1188 (C-O-C stretching), 1097 (C-H bending, aromatic), 729 (C-S stretching);^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.39 (s, 1H, TZD N-H), 8.91 (d, 2H, *J* = 6.48 Hz, 4-nitrophenyl), 8.07 (s, 1H, C=CH), 7.57 (d, 2H, *J* = 2.56 Hz, 4-nitrophenyl),4.91 (s, 2H, N-$\underline{CH_2}$-CO), 4.53 (s, 3H, OCH_3), 2.56 (s, 3H, CH_3);^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 178.27 (C_3, 1,3,5-triazin), 172.19 (C_2 TZD), 169.81 (C_3, 1,3,5-triazin), 166.74 (N-CH_2-$\underline{C}$O-NH), 162.24 (C_4, TZD), 152.19 (C_1, 1,3,5-triazin), 143.28 (C=$\underline{C}$H), 139.75, 133.33, 131.03, 117.07, (aromatic carbons), 55.87 (OCH_3), 49.47 (N-$\underline{C}H_2$-CO), 22.28 (CH_3); LC-MS(m/z): 401 M^+, 403 $[M+2]^+$.

(E)-2-(5-(furan-2-ylmethylene)-2,4-dioxothiazo lidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide C_3

IR (KBr) *v* cm^{-1}: 3327 (N-H stretching), 3145 (C-H stretching, aromatic), 3108, 3071, 2953 (C-H stretching, aliphatic), 2876 (C-H stretching, C=CH), 1757, 1739, 1690 (C=O stretching), 1597 (C=C stretching, aromatic), 1487 (C-H bending, CH_3), 1351 (C-H bending, CH_2), 1278 (C-N stretching), 1193 (C-O-C stretching), 1092 (C-H bending, aromatic),

691 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.67 (s, 1H, TZD N-H), 9.44 (d, 1H, *J* = 6.48 Hz, furfural), 8.50 (d, 1H, *J* = 6.92 Hz, furfural), 8.35 (s, 1H, C=CH), 6.77 (t, 1H, *J* = 1.80 Hz, furfural),4.52 (s, 2H, N-$\underline{CH_2}$-CO), 3.92 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 178.15 (C_3,1,3,5-triazin), 174.15 (C_2, TZD), 171.51 (C_2, 1,3,5-triazin), 168.84 (N-CH_2-$\underline{C}$O-NH), 162.43 (C_4, TZD), 151.97 (C_1, 1,3,5-triazin), 143.39 (aromatic carbons), 142.13 (C=$\underline{C}$H), 123.69, 123.03, 120.60 (aromatic carbons), 65.61 (OCH_3), 50.75 (N-$\underline{C}H_2$-CO), 25.63 (CH_3); LC-MS (m/z):390 M^+, 392 $[M+2]^+$.

(E)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-2-(5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide C_4

IR (KBr) *v* cm^{-1}: 3339 (N-H stretching), 3012 (C-H stretching, aromatic), 2987, 2883, 2846 (C-H stretching, aliphatic), 2824 (C-H stretching, C=CH), 1698, 1646 (C=O stretching), 1596 (C=C stretching, aromatic), 1494 (C-H bending, CH_3), 1488 (C-H bending, OCH_3), 1359 (C-H bending, CH_2), 1275 (C-N stretching), 1181 (C-O stretching), 758 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.57 (s, 1H, TZD N-H), 8.87 (d, 2H, *J* = 6.42 Hz, 4-methoxyphenyl),7.98 (s, 1H, C=CH), 7.56 (d, 2H, *J* = 2.48 Hz, 4-methoxyphenyl), 4.83 (s, 2H, N-$\underline{CH_2}$-CO), 4.58 (s, 3H, OCH_3), 4.69 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3);^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 176.78 (C_3, 1,3,5-triazin), 171.94 (C_2 TZD), 170.16 (C_3, 1,3,5-triazin), 166.43 (N-CH_2-$\underline{C}$O-NH), 161.93 (C_4, TZD), 152.43 (C_1, 1,3,5-triazin), 142.97 (C=$\underline{C}$H), 140.13, 132.28, 130.83, 128.94, 116.81, (aromatic carbons), 55.42 (OCH_3), 53.12 (OCH_3), 49.84 (N-$\underline{C}H_2$-CO), 22.83 (CH_3);LC-MS (m/z): 430 M^+, 432 $[M+2]^+$.

(E)-2-(2,4-dioxo-5-(pyridin-2-ylmethylene)thiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide C_5

IR (KBr) *v* cm^{-1}:3324 (N-H stretching), 3163 (C-H stretching, aromatic), 3072, 2958, 2912 (C-H stretching, aliphatic), 2870 (C-H stretching, C=CH), 1712, 1671(C=O stretching), 1593 (C=C stretching, aromatic), 1485 (C-H bending, CH_3), 1352 (C-H bending, CH_2), 1291 (C-N stretching), 1197 (C-O-C stretching), 1076 (C-H bending, aromatic), 679 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.58 (s, 1H, TZD N-H), 8.75 (d, 1H, *J* = 6.56 Hz, 2-pyridine),8.73 (t, 1H, *J* = 5.86 Hz, 2-pyridine), 8.72 (t, 1H, *J* = 5.66 Hz, 2-pyridine), 8.70 (d, 1H, *J* = 6.14 Hz, 2-pyridine), 8.03 (s, 1H, C=CH), 4.92 (s, 2H, N-$\underline{CH_2}$-CO), 4.64 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 178.92 (C_3, 1,3,5-triazin), 173.19 (C_2 TZD), 170.51 (C_3, 1,3,5-triazin), 166.76 (N-CH_2-$\underline{C}$O-NH), 163.12 (C_4, TZD), 152.03 (C_1, 1,3,5-triazin), 143.28 (C=$\underline{C}$H), 140.04, 137.18, 133.13, 129.06, 128.73, 127.85, 116.47, (aromatic carbons), 55.53 (OCH_3), 49.63 (N-$\underline{C}H_2$-CO), 22.43 (CH_3); LC-MS (m/z):401 M^+, 403 $[M+2]^+$.

(E)-2-(5-(4-chlorobenzylidene)-2,4-dioxothiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide C_6

IR (KBr) *v* cm^{-1}: 3338 (N-H stretching), 3145 (C-H stretching, aromatic), 3067, 2947, 2923 (C-H stretching, aliphatic), 2878 (C-H stretching, C=CH), 1724, 1679, 1641 (C=O stretching), 1597 (C=C stretching, aromatic), 1486 (C-H bending, CH_3), 1354 (C-H bending, CH_2), 1287 (C-N stretching), 1183 (C-O-C stretching), 1081 (C-H bending, aromatic), 824 (C-Cl stretching), 713 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.48 (s, 1H, TZD N-H), 8.87 (d, 2H, *J* = 6.56 Hz, 4-chlorophenyl),8.14 (s, 1H, C=CH), 7.64 (d, 2H, *J* = 2.68 Hz, 4-chlorophenyl),4.82 (s, 2H, N-$\underline{CH_2}$-CO), 4.58 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 179.68 (C_3, 1,3,5-triazin), 173.47 (C_2 TZD), 171.16 (C_3, 1,3,5-triazin), 167.77 (N-CH_2-$\underline{C}$O-NH), 161.98 (C_4, TZD), 153.17 (C_1, 1,3,5-triazin), 143.20 (C=$\underline{C}$H), 139.74, 133.43, 130.14, 128.83, 116.97, (aromatic carbons), 55.78 (OCH_3), 49.51 (N-$\underline{C}H_2$-CO), 22.27 (CH_3);LC-MS (m/z):435 M^+, 437 $[M+2]^+$, 439 $[M+4]^+$.

(E)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetamideC_7

IR (KBr) *v* cm^{-1}: 3335 (N-H stretching), 3017 (C-H stretching, aromatic), 3000, 2891, 2838 (C-H stretching, aliphatic), 2815 (C-H stretching, C=CH), 1687, 1648 (C=O stretching), 1602 (C=C stretching, aromatic), 1499 (C-H bending, CH_3), 1491 (C-H bending, OCH_3), 1355 (C-H bending, CH_2), 1282 (C-N stretching), 1177 (C-O stretching), 773 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (s, 1H, TZD N-H), 8.26 (d, 2H, *J* = 6.52 Hz, 4-methylphenyl),7.86 (s, 1H, C=CH), 7.42 (d, 2H, *J* = 2.76 Hz, 4-methyphenyl),4.63 (s, 2H, N-$\underline{CH_2}$-CO), 3.86 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 178.86 (C_3, 1,3,5-

triazin), 175.26 (C_2 TZD), 169.54 (C_3, 1,3,5-triazin), 164.68 (N-CH_2-CO-NH), 162.36 (C_4, TZD), 153.02 (C_1, 1,3,5-triazin), 143.68 (C=CH), 137.31, 131.25, 129.11, 128.24, 117.24, (aromatic carbons), 56.34 (OCH_3), 50.18 (N-CH_2-CO), 24.80 (CH_3), 21.60 (CH_3); LC-MS (m/z):415 M^+, 417 $[M+2]^+$.

(E)-2-(2,4-dioxo-5-(4-propylbenzylidene)thiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide C_8

IR (KBr) ν cm^{-1}: 3327 (N-H stretching), 3149 (C-H stretching, aromatic), 3105, 2962, 2927 (C-H stretching, aliphatic), 2853 C-H stretching, C=CH), 1764, 1679 (C=O stretching), 1585 (C=C stretching, aromatic), 1466 (C-H bending, CH_3), 1335 (C-H bending, CH_2), 1298 (C-N stretching), 1199 (C-O-C stretching), 1099 (C-H bending, aromatic), 743 (C-S stretching);^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.58 (s, 1H, TZD N-H), 8.78 (d, 2H, J = 6.64 Hz, 4-propylphenyl),7.64 (s, 1H, C=CH), 6.91 (d, 2H, J = 2.68 Hz, 4-propylphenyl),4.37 (s, 2H, N-CH_2-CO), 3.74 (s, 3H, OCH_3), 2.84 (t, 2H, J = 5.78 Hz, $CH_2CH_2CH_3$), 2.27 (s, 3H, CH_3), 1.73 (m, 2H, J = 8.12 Hz,$CH_2CH_2CH_3$), 0.94 (t, 3H, J = 6.14 Hz,$CH_2CH_2CH_3$);^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 179.82 (C_3, 1,3,5-triazin), 175.06 (C_2 TZD), 171.26 (C_3, 1,3,5-triazin), 165.72 (N-CH_2-CO-NH), 161.96 (C_4, TZD), 152.06 (C_1, 1,3,5-triazin), 143.32 (C=CH), 141.41, 135.62, 130.27, 128.24, 127.03, 115.31 (aromatic carbons), 56.34 (OCH_3), 48.82 (N-CH_2-CO), 38.34 ($CH_2CH_2CH_3$), 26.15($CH_2CH_2CH_3$), 22.24 (CH_3), 14.10 ($CH_2CH_2CH_3$);LC-MS (m/z): 443 M^+, 445 $[M+2]^+$.

2-((E)-2,4-dioxo-5-((Z)-3-phenylallylidene) thiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide C_9

IR (KBr) ν cm^{-1}: 3337 (N-H stretching), 3138 (C-H stretching, aromatic), 3092, 2969, 2924 (C-H stretching, aliphatic), 2858 C-H stretching, C=CH), 1773, 1676(C=O stretching), 1588 (C=C stretching, aromatic), 1461 (C-H bending, CH_3), 1343 (C-H bending, CH_2), 1302 (C-N stretching), 1181 (C-O-C stretching), 1084 (C-H bending, aromatic), 732 (C-S stretching); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.23 (s, 1H, TZD N-H), 8.71 (d, 2H, J = 6.58 Hz, phenyl), 7.93 (t, 2H, J = 8.48 Hz, phenyl), 7.68(t, 1H, J = 5.24 Hz, CHCHCH), 7.56 (d, 1H, J = 2.14 Hz,CHCHCH), 7.34 (d, 1H, J = 2.36 Hz, CHCHCH), 6.87 (d, 2H, J = 2.68 Hz, phenyl),4.33 (s, 2H, N-CH_2-CO), 3.78 (s, 3H, OCH_3);^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 177.18 (C_3, 1,3,5-triazin), 174.87 (C_2 TZD), 172.17 (C_3, 1,3,5-triazin), 166.04 (N-CH_2-CO-NH), 162.14 (C_4, TZD), 151.82 (C_1, 1,3,5-triazin), 145.09 (CH=CH=CH), 142.18, 140.87 (aromatic carbons), 137.31 (CH=CH=CH), 134.76 (CH=CH=CH), 128.63, 127.16, 114.97 (aromatic carbons), 57.14 (OCH_3), 48.73 (N-CH_2-CO), 22.24 (CH_3); LC-MS (m/z): 426 M^+, 428 $[M+2]^+$.

(E)-2-(5-(4-(dipropylamino)benzylidene)-2,4-dioxothiazolidin-3-yl)-N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamide C_{10}

IR (KBr) ν cm^{-1}: 3341 (N-H stretching), 3019 (C-H stretching, aromatic), 2997, 2889, 2836 (C-H stretching, aliphatic), 2819 (C-H stretching, C=CH), 1693, 1644 (C=O stretching), 1608 (C=C stretching, aromatic), 1486 (C-H bending, CH_3), 1463(C-H bending, OCH_3), 1356 (C-H bending, CH_2), 1279 (C-N stretching), 1181 (C-O stretching), 734 (C-S stretching);^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.67 (s, 1H,N-H), 10.31 (s, 1H, 4-dipropylaminophenyl), 8.74 (d, 2H, J = 6.52 Hz, 4-dipropylaminophenyl),7.60 (s, 1H, C=CH), 6.83 (d, 2H, J = 2.68 Hz, 4-dipropylaminophenyl),4.46 (s, 2H, N-CH_2-CO), 3.72 (s, 3H, OCH_3), 2.71 (t, 4H, J = 5.62 Hz, $CH_2CH_2CH_3$), 2.29 (s, 3H, CH_3), 1.79 (m, 4H, J = 8.48 Hz, $CH_2CH_2CH_3$), 0.95(t, 6H, J = 6.36 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 179.27 (C_3, 1,3,5-triazin), 173.93 (C_2 TZD), 171.31 (C_3, 1,3,5-triazin), 165.62 (N-CH_2-CO-NH), 161.68 (C_4, TZD), 152.28 (C_1, 1,3,5-triazin), 143.38 (C=CH), 140.87, 135.45, 130.19, 128.29, 127.13, 115.82 (aromatic carbons), 56.38 (OCH_3), 48.73 (N-CH_2-CO), 38.32 ($CH_2CH_2CH_3$), 26.18($CH_2CH_2CH_3$), 22.32 (CH_3), 14.18 ($CH_2CH_2CH_3$); LC-MS (m/z): 484 M^+, 486 $[M+2]^+$.

IR NMR and mass spectra of some selected compounds are given in Figs S1-S9 in Supplementary Information.

Results and Discussion

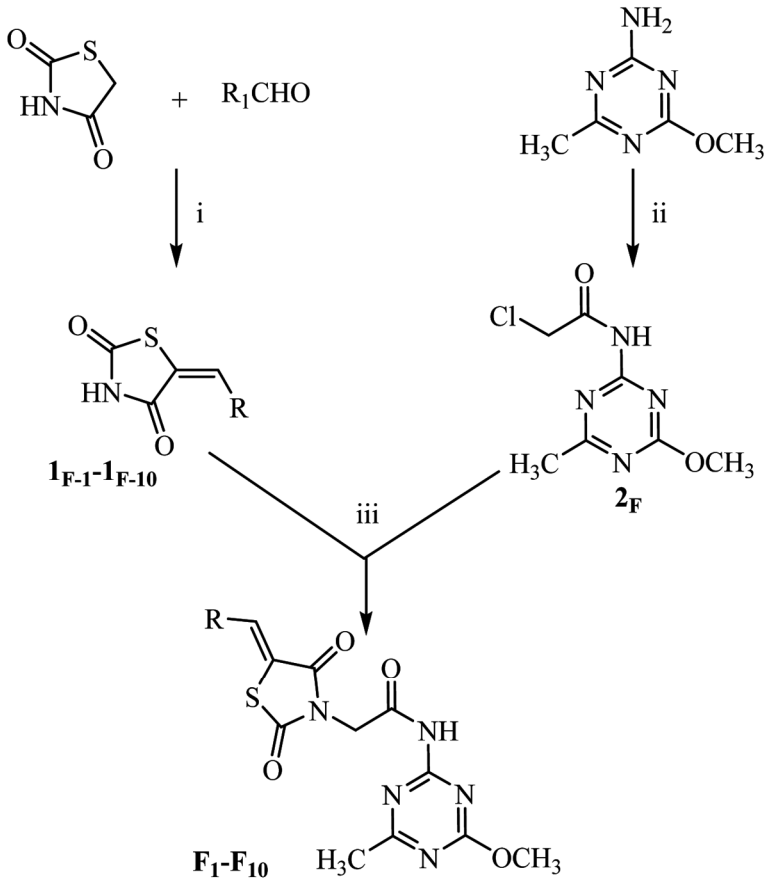
General chemistry

In present work, intermediate compounds (*E*)-5-substitutidenethiazolidine-2,4-dione(A_1-A_{10}) were synthesized by Knoevenagel condensation reaction held on Perkin-Elmer apparatus. Compounds (A_1-A_{10}) were reacted with 2-chloro-*N*-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)phenyl)acetamide (B) to give the final products (Z)-2-(5-ethylidene-2,4-dioxothiazo

lidin-3-yl)-*N*-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)acetamid (C_1-C_{10}). The general synthesis scheme of 2,4-thiazolidinedione derivatives (C_1-C_{10}) is depicted in Scheme 1. All the intermediates were purified by methanol and spectrally examined from IR and ^{1}H NMR spectra. Final compounds were crystallized from as usual solvent and spectrally examined from IR, ^{1}H NMR, ^{13}C NMR and Mass spectra. Solvents used in all steps were distilled out and dried it using dry sieves as the usual manner. 2D-QSAR prediction of the antitubercular activity as well as evaluation of antimicrobial and antitubercular activities of the synthesized compounds was done.

Antimicrobial activity

Broth dilution method was applied to quantitatively measure the *in vitro* antimicrobial activities against bacterial and fungal species[21,22]. Compounds were examined against two gram positive bacterial strains; *S. aureus* (MTCC-96) and *S. pyogenes* (MTCC-443), two gram-negative bacterial strains; *E. coli* (MTCC-442) and *P. aeruginosa* (MTCC-441), and for fungi, three species, *C. albicans* (MTCC-227), *A. niger* (MTCC-282), and *A. clavatus* (MTCC-1323). The strains and species were procured from Institute of Microbial Technology, Chandigarh. Minimum inhibitory concentrations (MICs) were calculated to evaluate the progresses of the compounds against microorganisms which considered the lowest concentration to evaluate antimicrobial agent to inhibit the visible growth of the microorganism. Chloramphenicol, ciprofloxacin and norfloxacin were used as reference drugs. The antibacterial results displayed in Table 3 revealed that the evicted compounds found to be active against different antifungal species were C_1 against *P. aeruginosa* and C_4



Reagents and conditions: (i) Piperidine, Glacial acetic acid, Toluene, Rf. 12-14 h.
(ii) Dichloromethane, Chloroacetyl chloride, TEA.
(iii) K_2CO_3 Rf. 4-5 h.

Scheme 1 — Synthesis of 2,4-thiazolidinedione derivatives (C_1-C_{10})

Table 3 — Antimicrobial activity of data compounds (C_1-C_{10})

Code	Minimal Bactericidal Concentration (µg/mL)				Minimal Fungicidal Concentration (µg/mL)		
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
	443	1688	96	442	227	228	1323
C_1	250	50	500	250	1000	500	1000
C_2	500	250	500	250	>1000	500	>1000
C_3	500	500	250	1000	500	>1000	>1000
C_4	125	500	50	500	500	>1000	>1000
C_5	250	500	500	250	1000	500	500
C_6	100	250	250	500	500	500	500
C_7	250	125	125	500	>1000	>1000	>1000
C_8	125	500	250	500	>1000	1000	>1000
C_9	125	250	250	500	>1000	>1000	>1000
C_{10}	250	500	500	250	500	1000	1000
Drug	Micromolar (µg/mL)						
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	25	25	50	50	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

All the MIC values presented as mean of six experiments. Antimicrobial activity is zero for 2% DMSO which used as control and diluent

against *S. aurius* when compared with the reference antibacterial drugs. The antifungal progressive values displayed in Table-3 which given the variable inhibitory effects against different fungal species.

Antitubercular activity

Antitubercular susceptibility progresses were denoted in MIC against *Mycobacterium tuberculosis H37Rv* which carried out applying L-J medium agar micro dilution method[23,24,25]. Rifampicin and isoniazid were used as reference drugs. The MIC levels of evicted compounds (C_1-C_{10}) against the organism were denoted in Table 4 which revealed that the compounds, demonstrated variable inhibitory effects on the growth of the evicted *M. tuberculosis H37Rv* strains. Among the evicted compounds C_7 and C_{10} were exhibited more active than others compounds and active when compared with rifampicin reference drug against *M. tuberculosis H37Rv*.

Structure activity relationship (SAR)

SAR observation suggested thiazolidine-2,4-dione, especially 3 and 5 substituted thiazolidine-2,4-dione more potent against antimicrobial and antitubercular activities[26,27]. At Position-3 toxophore((4-methoxy-6-methyl-1,3,5-triazin-2-yl)phenyl)acetamide provide the favourable enhancement against antimicrobial and antitubercular activities because of its having electron donating groups OCH_3 and CH_3which increases the electron density and resonance effects of the compounds. At position-5, C=C and substituted aromatic ring raised the antimicrobial progress due to increasing resonance. Toxophore thiazolidine-2,4-dione itself raised the antimicrobial progresses because of the presence of two carbonyl groups and electron pair having nitrogen and sulphur atoms. SAR study also suggested that all the synthesized lead targeted compounds having substitution 4-nitrophenyl and 4-methoxyphenyl are active against antibacterial activity. The compounds having 4-methylphenyl and

Table 4 — Antitubercular activity and 2D-QSAR data of compounds (C_1-C_{10})

Code	MIC (µg/mL)				Discriptors used
	Actual MIC	Actual pMIC	Predicted pMIC	Residual pMIC	T_2_2_0
C_1	100	-2.00	-2.05	-0.05	24.0478
C_2	250	-2.39	-2.39	0.00	24.0476
C_3	100	-2.00	-1.98	0.02	24.0394
C_4	500	-2.69	-2.68	0.01	24.0482
C_5	500	-2.69	-2.72	-0.03	24.0472
C_6	250	-2.39	-2.39	0.00	24.0594
C_7	1000	-3.00	-2.96	0.04	24.0598
C_8	1000	-3.00	-3.00	0.00	24.0479
C_9	250	-2.39	-2.44	-0.05	24.0474
C_{10}	100	-2.00	-2.01	-0.01	24.0420

pMIC(= 1/log MIC) value was used for 2D-QSAR determination. All the values of MIC presented as mean of six experiments. Antitubercular activity is zero for 2% DMSO which used as control and diluent. Conc. of Isonizid and Rifampicin are 0.20 and 40 µg/mL, respectively.

2-hydroxy-4-diethylaminophenyl substituents are more effective against antitubercular activity. The arrangement of groups and rings also affects better to good biological activities[28].

2D-QSAR

The 2D-QSAR study is useful to understand different biological characteristics and calculate the structural thermodynamic parameters which control the biological progresses. A number of thermodynamic parameters (physicochemical, spatial, electronic and topological) are normally useful for prediction of QSAR. The various thermodynamic descriptors calculate the free energy fluctuation because of the drug receptor complex. The topological structure descriptors are applied as an alignment independent descriptor. Both the independent descriptors are considered as independent variables. Spatial parameters are giving steric effect of the drug molecules which necessary to fit the drug with receptor. Non-covalent bonding between drug molecules and receptors describe electronic descriptor. QSAR resolution regression was carried out from applied pMIC values as dependent variables and calculated parameters as independent variables. Manually selecting and placing molecules in the training and test sets comprising of 8 and 2 molecules, respectively.

Partial least square regression method created significant QSAR model[29], which considered statistical parameters, correlation coefficient (r), squared correlation coefficient (r^2), predictive r^2 for external test set, (pred r^2) for external validation and Fischer's value (F). External validation (pred r^2) for the biological progression in the test set was predicted using the model created by the training set as calculated from the equation denoted from the reference[30].The cross-validated coefficient, q2, was calculated using the equation from the reference[31]. The significance of the models, hence obtained is derived based on a calculated Z score denoted from the reference[32].

pMIC (pMIC = log(1/MIC)) values and PLSR methodology were applied to the resolution of 2D-QSAR of *M. tuberculosis H37Rv* from VLife MDS software, which consider the term selection criterion as r^2, q^2, pred_r^2 and F test. The training and test sets of the compounds were selected by the sphere exclusion method and the models were validated by both internal and external validation procedures. The model gave the following equation for pMICs prediction.

Model equation

pMIC = -50.0000 T_2_2_0-1200.0000

$N_{training}$= 5, N_{test}= 5, Degree of freedom = 6, r^2 =0.3333, q^2 = 0.0400, F test = 3.0000, r^2_se = 70.7107, q^2_se = 84.8528, pred_r^2 = -1.9753, pred_r^2se = 274.4312.

The generated model has comparable to the previous model developed using manual selection with respect to training and internal validation and external validation. The equation explains 86% (r^2 = 0.8540) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2) predictive ability of ~61 % and ~62%, respectively. The F test = 35.09 shows the statistical significance of 99.99% of the model which means that probability of failure of the model is 1 in 10000.The model incorporates parameter T_2_2_O their corresponding values for each molecule in the selected model, which indices oxygen atom attached with double bond inversely proportional to compounds activity. The negative sign influencing activity variation is inversely proportional to activity. The model is validated by Z_{Score} $R^{\wedge 2}$ = -1. Z_{Score} $Q^{\wedge 2}$ = 0.94868, Best Rand $R^{\wedge 2}$ 0.3333, Best Rand $Q^{\wedge 2}$ = 0.04000, Alpha Rand $R^{\wedge 2}$ = 99.00000, Alpha Rand $Q^{\wedge 2}$ = 99.00000, Z_{Score}Pred $R^{\wedge 2}$-1. Best Rand Pred $R^{\wedge}$= 0.69136, Alpha Rand Pred $R^{\wedge 2}$ = 0.0000. The randomization test suggests that the developed model has a probability of less than 1% that the model is generated by chance. The observed and predicted pMIC along with residual values and used descriptors are shown in Table 4. Fitness graph predicted vs actual data given in Fig. 1.

It is mandatory to study the pharmacokinetics properties, i.e., absorption in the body, distribution into the different compartments, metabolism by organs and elimination through the body. Computational studies of the ADME parameters are mandatory to design the molecules which prioritize for synthesis[33]. Hence, *in silico* ADME study is an essential step for checking the drug-likeness. ADME studies of the synthesised compounds (C_1-C_{10}) were carried out using the Swiss ADME tool [34]. QSAR studies and drug-likeness are also predicted to know the octanol/ water partition coefficient (log $P_{o/w}$), Topological polar surface area (TPSA), Hydrogen bond Acceptor (HBA), Hydrogen Bond Donor (HBD), Lipinski Rule and synthetic accessibility are tabulated in Table 5**.**

Lipinski rule of five is given by Lipinski[35] in 1997, the rule of five is based on certain criteria to estimate drug-likeness of a molecule having a pharmacological activity. These criteria are log P lower than 5, number of HBD<5, HBA<10 and M.W not exceeding 500 Da. The rule is used in drug design to preselect molecules presenting good absorption, distribution, metabolism, and excretion (ADME) properties that must have a medicament in the organism. We have used the ADME property calculator (http://www.SwissADME .com) to calculate the four parameters of Lipinski's rule in addition to the number of rotatable bonds that have to be inferior to 10 to have a good oral bioavailability[36].

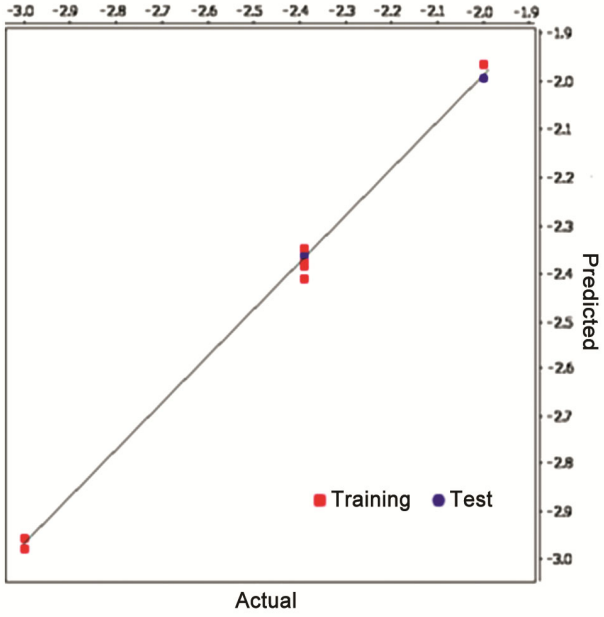


Fig. 1 — Activity distribution graph for predicted vs actual data of compounds (C_1-C_{10})

Conclusion

Synthesis of thiazolidine-2,4-dione and 4-methoxy-6-methyl-1,3,5-triazin-2-amine clubbed biologically active conjugates (*Z*)-2-(5-substituted ene-2,4-dioxothiazolidin-3-yl)-*N*-(4-methoxy-6-met hyl-1,3,5-triazin-2-yl)acetamid(C_1-C_{10}). These deriv atives have thiazolidine-2,4-dione and 4-methoxy-6-methyl-1,3,5-triazin-2-amine as antimicrobial and antitubercular toxophores which increase the biological activities. From the biological results, 4-nitrobenzene and 4-methylbenzene are active against different antimicrobial species and 4-methylphenyl and 2-hydroxy-4-diethylaminophenyl containing compounds more effective against antitubercular activity. 2- dimensional structure activity relationship (2D-QSAR) for *M. tuberculosis H37Rv* from VLife MDS software were also carried out. 2D-QSAR resolution suggested that antitubercular activity is inversely correlated with descriptor T_2_2_O with their corresponding values for each molecule. All active compounds followed the Lipinski rule.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Table 5 — *In silico* admet properties data of the compounds (C_1-C_{10})

Code	RB	HBA	HBD	MR	Log S	GI absorption & BBB Permeant	Log Kp (cm/s)	SA	TPSA	Lipinski rule
C_1	7	9	1	113.53	-3.12	Low & No	-8.07	4.17	179.41	1
C_2	6	8	1	96.50	-2.59	Low & No	-8.06	3.84	152.57	0
C_3	6	8	1	91.80	-2.41	High & No	-7.99	3.39	127.52	0
C_4	6	7	1	107.67	-3.96	High & No	-6.79	3.75	139.68	0
C_5	7	8	1	109.20	-3.73	Low & No	-7.17	3.70	148.91	0
C_6	6	8	1	100.50	-3.01	Low & No	-7.71	3.69	152.57	0
C_7	6	7	1	107.72	-4.25	High & No	-6.73	3.62	139.68	0
C_8	8	7	1	117.29	-4.60	Low & No	-6.27	3.89	139.68	0
C_9	7	7	1	111.85	-4.14	High & No	-6.67	3.84	139.68	0
C_{10}	9	8	2	125.38	-3.45	Low & No	-7.82	3.86	137.85	1

RB: Rotatable Bond, HBA: Hydrogen bond acceptors, HBD: Hydrogen bond donors, MR: Molar Refractive, SA: Synthetic Accessibility, TPSA: Topologocal Polar Surface Area

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