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SYNTHESIS, SCREENING AND QSAR STUDIES OF 3-BENZOYL-2-OXO/THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE ANALOGUES AS ANTIBACTERIAL AGENTS

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ABSTRACT. The purpose of this study was to synthesize several 3-benzoyl-5-acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines, evaluate them for their antibacterial activity and to establish correlation between the activity and physicochemical properties. 5-Acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines (**A**) were synthesized by cyclocondensation reaction between appropriate aldehyde, acetoacetate and urea/thiourea in presence of aluminium chloride and hydrochloric acid which upon treatment with benzoyl chloride in presence of pyridine in benzene furnish the title compounds (**1-28**). The structures of all title compounds have been confirmed on the basis of their analytical, IR and NMR spectral data. The title compounds have been tested for antibacterial activity against *Staphylococcus aureus*. The compounds were divided into training and test sets. A quantitative structure activity relationship study was made using various descriptors. Several statistical expressions were developed using stepwise multiple linear regression analysis. The best quantitative structure activity relationship model was further cross validated. The study revealed that total positive partial charge (PC+) and total polar negative Van der Waals surface area (Q_VSA_PNEG) contributes negatively where as contribution of Van der Waals surface area to molar refractivity (SMR_VSA7) contributes positively to the antibacterial activity. The compounds with improved antibacterial potential can be successfully designed with selected quantitative structure activity relationship model.

KEY WORDS: 2-Oxo/thioxo-1,2,3,4-tetrahydropyrimidines, Antibacterial, QSAR

INTRODUCTION

In recent years, substituted 2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines received significant attention owing to their diverse range of biological properties such as calcium channel modulator [1], 1-adrenoreceptor selective antagonist [2], HIV gpl20-CD_4 inhibition [3], antiviral [4], oral antihypertensive [5], useful for the treatment of benign prostatic hyperplasia [6], anti-inflammatory [7], Muscarinic [8], antifungal and antibacterial [9]. The presence of several interacting functional groups in these compounds also determines their great synthetic potential [10].

The resistance of common pathogens to standard antibiotic therapy is rapidly becoming a major health problem throughout the world. The resistance of multidrug-resistant gram-positive bacteria is increasing and infections caused by *Staphylococcus aureus*, *enterococci* and *pneumococci* are particularly problematic [11]. There is a real perceived need for the discovery of new compounds endowed with antibacterial property.

QSAR studies of antimicrobial activity represent an emerging and exceptionally important topic in the area of computer-aided drug design. QSAR models are highly effective in describing the structural basis of biological activity. It is now widely used for the prediction of physicochemical properties and biological activities in chemical, environmental and pharmaceutical areas. 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 compounds without the need to synthesis and test them.

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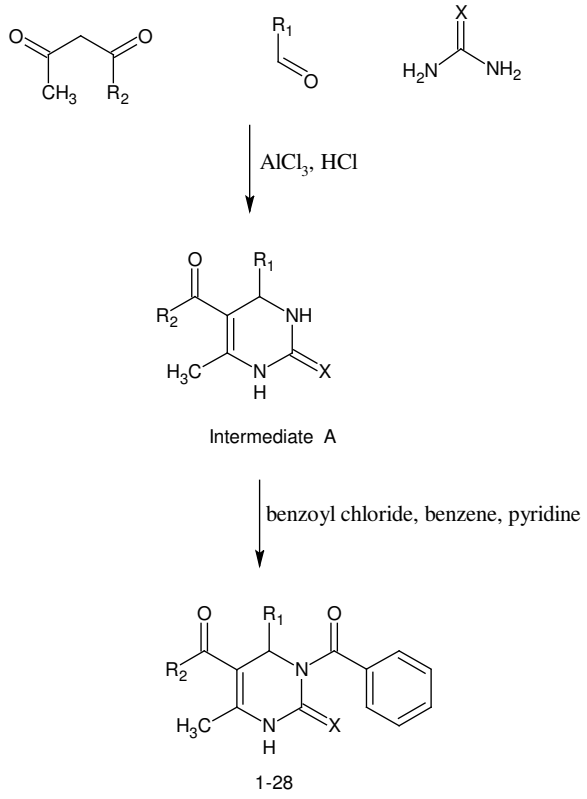
In the present paper we describe the synthesis, screening and QSAR studies to investigate the relationship between the various physicochemical parameters and antibacterial activity of synthesized 3-benzoyl derivatives of 5-acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines.

EXPERIMENTAL

Melting points of the synthesized compounds were determined in open capillary tubes are therefore uncorrected. The structures of the title compounds were established on the basis of elemental analysis and spectral data. The IR spectra were recorded on JASCO FTIR 4100 spectrophotometer. ^{1}H NMR spectra were recorded on Varian NMR 400 MHz spectrometer using $CDCl_3$/DMSO-d_6 as solvent with TMS as an internal standard. Purity of the synthesized compounds was checked by silica gel – G plate using benzene and ethyl acetate as developer.



Synthesis scheme

General procedure for the synthesis of 5-acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines **(A)**

These compounds were synthesized by the reported cyclocondensation reaction [12-13] between aldehyde, acetoacetate and urea/thiourea. The mixture of appropriate aldehyde (0.02 mole), acetoacetate (0.02 mole), urea/thiourea (0.03 mole), aluminium chloride (0.01 mole), conc.

hydrochloric acid (2 drops) in methanol (20 mL) were refluxed for 4 h. The solid thus separated on cooling was filtered, washed with cold methanol, dried and recrystallized from methanol.

General procedure for the synthesis of 3-benzoyl derivatives of 5-acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines **(1-28)**

To a suspension of respective 5-acyl-6-methyl-4-substituted-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine **A** (0.02 mole) and pyridine (4 mL) in dry benzene (20 mL), benzoyl chloride (0.03 mole) was added drop wise at room temperature. The resulting solution was heated to reflux for 2 h. After cooling water (80 mL) was added and allowed benzene layer to separate. Benzene layer was washed with sodium carbonate solution (5 % w/v) followed by water and treated with anhydrous magnesium sulphate. Supernatant benzene layer after decantation was concentrated to obtain oily residue which upon recrystallization with methanol yield solid product.

Ethyl 3-benzoyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(1)**. Yield: 66.43 %; m.p.: 202 ^{o}C; IR (KBr, cm^{-1}): 3240, 3140 (N-H), 2970 (C-H), 1720 (C=O), 1700 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.25 (s, 3H, C_6–CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2), 6.62 (s, 1H, methine CH), 7.40-7.44 (m, 5H, Ph), 7.77-7.90 (m, 5H, COPh), 9.39 (s, 1H, NH). Anal. calcd. for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69 %. Found: C, 69.18; H, 5.47; N, 7.62 %.

Ethyl 3-benzoyl-4-(4-dimethylaminophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(2)**. Yield: 50.00 %; m.p.: 240 ^{o}C; IR (KBr, cm^{-1}): 3245, 3140 (N-H), 2980 (C-H), 1710 (C=O), 1695 (C=O), 1685(C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (t, J = 7 Hz, 3H, ethyl CH_3), 2.25 (s, 3H, C_6–CH_3), 2.83 (s, 6H, $N(CH_3)_2$, 3.99 (q, J = 7 Hz, 2H, OCH_2), 6.62 (s, 1H, methine CH), 6.43-7.24 (m, 4H, Ph), 7.50-7.90 (m, 5H, COPh), 9.40 (s, 1H, NH). Anal. calcd. for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31 %. Found: C, 67.74; H, 6.12; N, 10.27 %.

Ethyl 3-benzoyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(3)**. Yield: 72 %; m.p.: 164 ^{o}C; IR (KBr, cm^{-1}): 3250, 3145 (N-H), 2975 (C-H), 1715 (C=O), 1695 (C=O), 1685 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.25 (s, 3H, C_6–CH_3), 3.60 (s, 3H, OCH_3), 3.99 (q, J = 7 Hz, 2H, OCH_2), 6.62 (s, 1H, methine CH), 6.92-7.34 (m, 4H, Ph), 7.52-7.90 (m, 5H, COPh), 9.38 (s, 1H, NH). Anal. calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10 %. Found: C, 66.94; H, 5.58; N, 7.08 %.

Ethyl 3-benzoyl-6-methyl-2-oxo-4-[(E)-2-phenylvinyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(4)**. Yield: 76.00 %; m.p.: 156 °C; IR (KBr, cm^{-1}): 3225, 3105 (N-H), 2990 (C-H), 1730 (C=O), 1715 (C=O), 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.26 (s, 3H, C_6–CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2), 6.02 (s, 1H, methine CH), 7.15 (s, 1H, Ph-CH), 7.20 (s, 1H, CH-C_6), 7.27-7.32 (m, 5H, Ph), 7.75-7.92 (m, 5H, COPh), 8.84 (s, 1H, NH). Anal. calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17 %. Found: C, 70.69; H, 5.63; N, 7.13 %.

Ethyl 3-benzoyl-4-(2-furyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(5)** Yield: 40.00 %: m.p.: 180 °C; IR (KBr, cm^{-1}): 3240, 3120 (N-H), 2980 (C-H), 1720 (C=O), 1710 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.25 (s, 3H, C_6-CH_3), 3.99 (q, J = 7 Hz, 2H, OCH_2), 5.80-6.32 (m, 3H, furan), 6.65 (s, 1H, methine CH), 7.77-7.90 (m, 5H, COPh), 8.57 (s, 1H, NH). Anal. calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.19 %. Found: C, 64.34; H, 5.08; N, 7.14 %.

Ethyl 3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**6**). Yield: 61.90 %; m.p.: 212 °C; IR (KBr, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1720 (C=O), 1700 (C=O), 1690 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, J = 7 Hz, 3H, ethyl CH_3), 2.25 (s, 3H, C_6–CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2), 6.78 (s, 1H, methine CH), 6.80-7.35 (m, 4H, Ph), 7.77-7.90 (m , 5H, COPh), 9.40 (s, 1H, NH), 10.65 (s, 1H, Ar-OH). Anal. calcd. for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36 %. Found: C, 66.28; H, 5.24; N, 7.31 %.

Methyl 3-benzoyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7**). Yield: 67.60 %; m.p.: 202 °C; IR (KBr, cm^{-1}): 3240, 3140 (N-H), 2970 (C-H), 1720 (C=O), 1690 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, C_6–CH_3), 3.71 (s, 3H, $COOCH_3$), 6.62 (s, 1H, methine CH), 7.20-7.44 (m, 5H, Ph), 7.76-7.90 (m , 5H, COPh), 9.38 (s, 1H, NH). Anal. calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00 %. Found: C, 68.51; H, 5.15; N, 7.94 %.

Methyl 3-benzoyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(8)**. Yield: 54.55 %; m.p.: 270°C; IR (KBr, cm^{-1}): 3260, 3125 (N-H), 2965 (C-H), 1710 (C=O), 1695 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (s, 3H, C_6–CH_3), 3.70 (s, 3H, $COOCH_3$), 5.07 (s, 2H, methylene CH_2), 7.48-7.87 (m, 5H, COPh), 9.40 (s, 1H, NH). Anal. calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21 %. Found: C, 61.28; H, 5.08; N, 10.18 %.

Methyl 3-benzoyl-6-methyl-2-oxo-4-[(E)-2-phenylvinyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**9**). Yield: 69.90 %; m.p.: 170 °C; IR (KBr, cm^{-1}): 3225, 3105 (N-H), 2990 (C-H), 1725 (C=O), 1715 (C=O), 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.26 (s, 3H, C_6–CH_3), 3.71 (s, 3H, $COOCH_3$), 6.02 (s, 1H, methine CH), 7.15 (s, 1H, Ph-CH), 7.20 (s, 1H, CH-C_6), 7.27-7.32 (m, 5H, Ph), 7.75-7.92 (m, 5H, COPh), 8.84 (s, 1H, NH). Anal. calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.14 %. Found: C, 70.17; H, 5.32; N, 7.11 %.

Methyl 3-benzoyl-4-(2-furyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(10)**. Yield: 43.52 %; m.p.: 270 °C; IR (KBr, cm^{-1}): 3240, 3120 (N-H), 2980 (C-H), 1720 (C=O), 1710 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.25 (s, 3H, C_6-CH_3), 3.71 (s, 3H, $COOCH_3$), 5.80-6.32 (m, 3H, furan), 6.65 (s, 1H, methine CH), 7.77-7.90 (m, 5H, COPh), 8.57 (s, 1H, NH). Anal. calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23 %. Found: C, 63.48; H, 4.69; N, 8.19 %.

Methyl 3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(11)**. Yield: 61.90 %; m.p.: 212 °C; IR (KBr, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1700 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H, C_6–CH_3), 3.71 (s, 3H, $COOCH_3$), 6.78 (s, 1H, methine CH), 6.80-7.38 (m, 4H, Ph), 7.77-7.90 (m, 5H, COPh), 9.41 (s, 1H, NH), 10.65 (s, 1H, Ar-OH). Anal. calcd. for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65 %. Found: C, 65.53; H, 4.93; N, 7.61 %.

5-Acetyl-3-benzoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **(12)**. Yield: 32.11 %; m.p.: 220 °C; IR (KBr, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1700 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H, C_6–CH_3), 2.33 (s, 3H, $COCH_3$), 6.91 (s, 1H, methine CH), 7.20-7.60 (m, 5H, Ph), 7.88-7.90 (m, 5H, COPh), 9.41 (s, 1H, NH). Anal. calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38 %. Found: C, 71.79; H, 5.38; N, 8.35 %.

5-Acetyl-3-benzoyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(13)**. Yield: 65.87 %; m.p.: 257 °C; IR (KBr, cm^{-1}): 3260, 3125 (N-H), 2965 (C-H), 1710 (C=O), 1695 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H, C_6–CH_3), 2.31 (s, 3H, $COCH_3$), 5.46 (s, 2H, methylene

CH_2), 7.50-7.87 (m, 5H, COPh), 9.40 (s, 1H, NH). Anal. calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85 %. Found: C, 65.09; H, 5.42; N, 10.82 %.

5-Acetyl-3-benzoyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(14)**. Yield: 12.62 %; m.p.: 238 °C; IR (KBr, cm^{-1}): 3245, 3140 (N-H), 2980 (C-H), 1710 (C=O), 1695 (C=O), 1685 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.11 (s, 3H, C_6–CH_3), 2.33 (s, 3H, $COCH_3$), 2.83 (s, 6H, $N(CH_3)_2$, 6.91 (s, 1H, methine CH), 6.49-7.25 (m, 4H, Ph), 7.50-7.90 (m, 5H, COPh), 9.40 (s, 1H, NH). Anal. calcd. for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13 %. Found: C, 69.08; H, 6.11; N, 11.09 %.

5-Acetyl-3-benzoyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(15)**. Yield: 60.95 %; m.p.: 166 °C; IR (KBr, cm^{-1}): 3250, 3145 (N-H), 2975 (C-H), 1715 (C=O), 1695 (C=O), 1685 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H, C_6–CH_3), 2.33 (s, 3H, $COCH_3$), 3.60 (s, 3H, OCH_3), 6.91 (s, 1H, methine CH), 6.98-7.34 (m, 4H, Ph), 7.50-7.90 (m, 5H, COPh), 9.38 (s, 1H, NH). Anal. calcd. for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69 %. Found: C, 64.33; H, 5.48; N, 7.65 %.

5-Acetyl-3-benzoyl-6-methyl-4-[(E)-2-phenylvinyl]-3,4-dihydropyrimidin-2(1H)-one **(16)** Yield: 68.57 %; m.p.: 190 °C; IR (KBr, cm^{-1}): 3225, 3105 (N-H), 2990 (C-H), 1725 (C=O), 1715 (C=O), 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H, C_6–CH_3), 2.34 (s, 3H, $COCH_3$), 6.45 (s, 1H, methine CH), 7.15 (s, 1H, Ph-CH), 7.30 (s, 1H, CH-C_6), 7.27-7.32 (m, 5H, Ph), 7.81-7.92 (m, 5H, COPh), 8.84 (s, 1H, NH). Anal. calcd. for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77 %. Found: C, 73.28; H, 5.55; N, 7.74 %.

5-Acetyl-3-benzoyl-4-(2-furyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(17)**. Yield: 54.55 %; m.p.: 220 °C; IR (KBr, cm^{-1}): 3240, 3120 (N-H), 2980 (C-H), 1720 (C=O), 1710 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.12 (s, 3H, C_6-CH_3), 2.33 (s, 3H, $COCH_3$), 5.80-6.82 (m, 3H, furan), 6.66 (s, 1H, methine CH), 7.88-7.90 (m, 5H, COPh), 8.57 (s, 1H, NH). Anal. calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64 %. Found: C, 66.62; H, 4.94; N, 8.61 %.

5-Acetyl-3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(18)** Yield: 12.15 %; m.p.: 198 °C; IR (KBr, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1700 (C=O), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H, C_6–CH_3), 2.33 (s, 3H, $COCH_3$), 6.85-7.38 (m, 4H, Ph), 7.08 (s, 1H, methine CH), 7.88-7.90 (m, 5H, COPh), 9.41 (s, 1H, NH), 10.65 (s, 1H, Ar-OH). Anal. calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00 %. Found: C, 68.52; H, 5.13; N, 7.96 %.

Ethyl 3-benzoyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(19)**. Yield: 66.17 %; m.p.: 160 °C; IR (KBr, cm^{-1}): 3240, 3140 (N-H), 2970 (C-H), 1720 (C=O), 1700 (C=O), 1520 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, J = 7 Hz, 3H, ethyl CH_3), 2.08 (s, 3H, C_6–CH_3), 3.99 (q, J = 7 Hz, 2H, OCH_2), 6.69 (s, 1H, methine CH), 7.42-7.44 (m, 5H, Ph), 7.76-7.77 (m, 5H, COPh), 9.39 (s, 1H, NH). Anal. calcd. for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36 %. Found: C, 66.21; H, 5.20; N, 7.27 %.

Ethyl 3-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(20)**. Yield: 42.80 %; m.p.: 132 °C; IR (KBr, cm^{-1}): 3260, 3130 (N-H), 2960 (C-H), 1715 (C=O), 1690 (C=O), 1525 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (t, J = 7 Hz, 3H, ethyl CH_3), 2.31 (s, 3H, C_6–CH_3), 4.10 (q, J = 7 Hz, 2H, OCH_2), 6.20 (s, 2H, methylene CH_2), 7.67-7.88 (m, 5H, COPh), 9.41 (s, 1H, NH). Anal. calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20 %. Found: C, 59.15; H, 5.22; N, 9.24 %.

Ethyl 3-benzoyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(21)**. Yield: 42.10 %; m.p.: 121 ^{o}C; IR (KBr, cm^{-1}): 3250, 3145 (N-H), 2975 (C-H), 1715 (C=O), 1695 (C=O), 1510 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.08 (s, 3H, C_6–CH_3), 3.60 (s, 3H, OCH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2), 6.69 (s, 1H, methine CH), 6.69-7.36 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.38 (s, 1H, NH). Anal. calcd. for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82 %. Found: C, 64.33; H, 5.35; N, 6.78 %.

Ethyl 3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(22)**. Yield: 45.54 %; m.p.: 120^{o}C; IR (KBr, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.08 (s, 3H, C_6–CH_3), 3.97 (q, J = 7 Hz, 2H, OCH_2), 6.85 (s, 1H, methine CH), 6.78-6.95 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.03 (s, 1H, Ar-OH), 9.40 (s, 1H, NH). Anal. calcd. for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07 %. Found: C, 63.56; H, 4.01; N, 7.02 %.

Ethyl 3-benzoyl-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(23)**. Yield: 39.00 %; m.p.: 140 ^{o}C; IR (KBr, cm^{-1}): 3245, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S); ^{1}H NMR (400 MHz) δ: 1.11 (t, J = 7 Hz, 3H, ethyl CH_3), 2.08 (s, 3H, C_6–CH_3), 3.99 (q, J = 7 Hz, 2H, OCH_2), 6.69 (s, 1H, methine CH), 6.77-7.34 (m, 4H, Ph), 7.71-7.77 (m , 5H, COPh), 9.04 (s, 1H, Ar-OH), 9.41 (s, 1H, NH). Anal. calcd. for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07 %. Found: C, 63.57; H, 4.98; N, 7.01 %.

Methyl 3-benzoyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**24**). Yield: 48.00 %; m.p.: 190 ^{o}C; IR (KBr, cm^{-1}): 3240, 3140 (N-H), 2970 (C-H), 1720 (C=O), 1690 (C=O), 1510 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H, C_6–CH_3), 3.71 (s, 3H, $COOCH_3$), 6.69 (s, 1H, methine CH), 7.20-7.44 (m, 5H, Ph), 7.76-7.77 (m , 5H, COPh), 9.38 (s, 1H, NH). Anal. calcd. for $C_{20}H_{18}N_2O_3S$: C, 65.55; H, 4.95; N, 7.64 %. Found: C, 65.51; H, 4.87; N, 7.57 %.

Methyl 3-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(25)**. Yield: 40.50 %; m.p.: 150 ^{o}C; IR (KBr, cm^{-1}): 3260, 3125 (N-H), 2965 (C-H), 1710 (C=O), 1690 (C=O), 1515 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H, C_6–CH_3), 3.70 (s, 3H, $COOCH_3$), 6.20 (s, 2H, methylene CH_2), 7.67-7.75 (m, 5H, COPh), 9.40 (s, 1H, NH). Anal. calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65 %. Found: C, 57.87; H, 4.82; N, 9.61 %.

Methyl 3-benzoyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(26)**. Yield: 50.50 %; m.p.: 164 ^{o}C; IR (KBr, cm^{-1}): 3220, 3100 (N-H), 2980 (C-H), 1705 (C=O), 1690 (C=O), 1510 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H, C_6–CH_3), 3.60 (s, 3H, OCH_3), 3.71 (s, 3H, $COOCH_3$), 6.69 (s, 1H, methine CH), 6.95-7.36 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.38 (s, 1H, NH). Anal. calcd. for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07 %. Found: C, 63.58; H, 5.03; N, 7.01 %.

Methyl 3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(27)**. Yield: 40.00 %; m.p.: 200 ^{o}C; IR (KBr, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H, C_6–CH_3), 3.71 (s, 3H, $COOCH_3$), 6.85 (s, 1H, methine CH), 6.78-7.28 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.03 (s, 1H, Ar-OH), 9.41 (s, 1H, NH). Anal. calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.33 %. Found: C, 62.79; H, 4.71; N, 7.29 %.

Methyl 3-benzoyl-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-Carboxylate **(28)**. Yield: 51.47 %; m.p.: 165 ^{o}C; IR (KBr, cm^{-1}): 3240, 3100 (N-H), 2980 (C-H),

1715 (C=O), 1680 (C=O), 1520 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H, C_6–CH_3), 3.71 (s, 3H, $COOCH_3$), 6.69 (s, 1H, methine CH), 6.77-7.34 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.05 (s, 1H, Ar-OH), 9.42 (s, 1H, NH). Anal. calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.33 %. Found: C, 62.78; H, 4.69; N, 7.28 %.

Antibacterial activity

Antibacterial activity of these twenty eight compounds was tested *in vitro* against gram-positive bacteria *Staphylococcus aureus* (NCIM-2079) by the cup-plate agar diffusion method, using dimethyl sulfoxide as solvent and trimethoprim as standard drug. Further minimum inhibitory concentration (MIC) of all these compounds was determined by double dilution method [14]. The biological data minimum inhibitory concentration (MIC) in mg/mL were converted to negative logarithmic dose in moles (pMIC) for QSAR analysis.

QSAR analysis

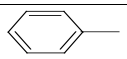
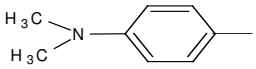
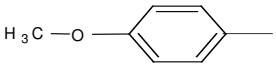
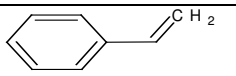
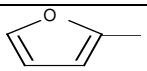
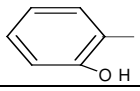
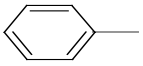
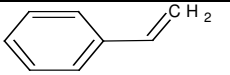
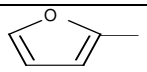
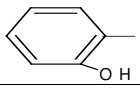
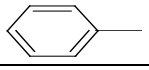
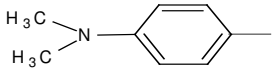
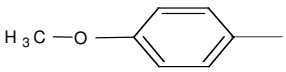
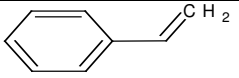
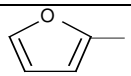
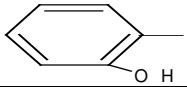
The series was subjected to QSAR analysis using MOE 2006.08 running on P-IV processor. The compounds were divided into training and test sets each consisting of 18 and 10 molecules, respectively. The training set was used for the model development and test set was used for cross validation of QSAR model developed by the training set. Structures of all the compounds were sketched using builder module of the programme. These structures were then subjected to energy minimization using Hamiltonian force field molecular mechanics-MMFF 94X by fixing root mean square (RMS) gradient as 0.01 kcal/mol Å. The descriptor values for all the molecules were calculated using "compute descriptor" module of the programme. All the calculated descriptors were considered as independent variable and biological activity (pMIC) as dependent variable. Stepwise multiple linear regression analysis method was used to perform QSAR analysis to generate several models. The best model was selected on the basis of various statistical parameters such as squared correlation coefficient (r^2), standard error of estimation (SE), sequential Fischer test (F). Quality and predictability of model was estimated from the cross validated squared correlation coefficient (q^2) [15-16].

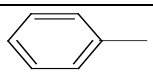
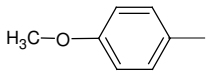
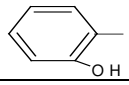
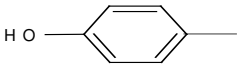
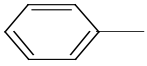
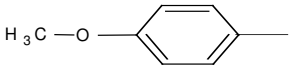
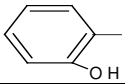
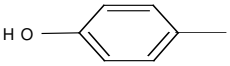
RESULTS AND DISCUSSION

The purity and homogeneity of all the title compounds were confirmed by their sharp melting points and TLC. In all cases these compounds were obtained in solid state. The synthesized compounds were subjected to physico-chemical characterization (Table 1) and elemental analysis. The structures of these compounds were confirmed by C, H and N analytical data, IR and ^{1}H NMR spectral data. Antimicrobial activity data against *Staphylococcus aureus* minimum inhibitory concentration (MIC) in mg/mL was converted to negative logarithmic dose in moles (pMIC) for QSAR analysis (Table 2). Values of descriptors (Table 3) which are significant in model are showing high correlation with biological activity. The inter correlation among the descriptor and their correlation with antibacterial activity is demonstrated by construction of correlation matrix (Table 4). Performing stepwise multiple linear regression analysis results in several equations out of that following four are found to be statistically significant QSAR models.

$$\begin{aligned} \text{pMIC} = {} & 4.97312 + 0.04823\ (\pm 0.0231)^*\ \text{PEOE\_VSA\_PNEG} - 0.02076\ (\pm 0.0061)^* \\ & \text{PEOE\_VSA\_PPOS} - 1.85275\ (\pm 0.3356)^*\ \text{FCASA-} \\ & n = 18,\ r^2 = 0.73706,\ q^2 = 0.564376,\ SE = 0.2372,\ F = 13.08,\ p = 0.0002 \end{aligned} \quad (1)$$

Table 1. Characterization data of the title compounds (1-28).

Compound	R_1	R_2	X	Mol. formula	Yield (%)	M.P. (^oC)
1		OC_2H_5	O	$C_{21}H_{20}N_2O_4$	66.43	202
2		OC_2H_5	O	$C_{23}H_{25}N_3O_4$	50.00	240
3		OC_2H_5	O	$C_{22}H_{22}N_2O_5$	72.00	164
4		OC_2H_5	O	$C_{23}H_{22}N_2O_4$	76.00	156
5		OC_2H_5	O	$C_{19}H_{18}N_2O_5$	40.00	180
6		OC_2H_5	O	$C_{21}H_{20}N_2O_5$	30.10	172
7		OCH_3	O	$C_{20}H_{18}N_2O_4$	67.60	202
8	H	OCH_3	O	$C_{14}H_{14}N_2O_4$	54.55	270
9		OCH_3	O	$C_{22}H_{20}N_2O_4$	69.90	170
10		OCH_3	O	$C_{18}H_{16}N_2O_5$	43.52	270
11		OCH_3	O	$C_{20}H_{18}N_2O_5$	61.90	212
12		CH_3	O	$C_{20}H_{18}N_2O_3$	32.11	220
13	H	CH_3	O	$C_{14}H_{14}N_2O_3$	65.87	257
14		CH_3	O	$C_{22}H_{23}N_3O_3$	12.62	238
15		CH_3	O	$C_{21}H_{20}N_2O_4$	60.95	166
16		CH_3	O	$C_{22}H_{20}N_2O_3$	68.57	190
17		CH_3	O	$C_{18}H_{16}N_2O_4$	54.55	220
18		CH_3	O	$C_{20}H_{18}N_2O_4$	12.15	198

19		OC_2H_5	S	$C_{21}H_{20}N_2O_3S$	66.17	160
20	H	OC_2H_5	S	$C_{15}H_{16}N_2O_3S$	42.80	132
21		OC_2H_5	S	$C_{22}H_{22}N_2O_4S$	42.10	121
22		OC_2H_5	S	$C_{21}H_{20}N_2O_4S$	45.54	120
23		OC_2H_5	S	$C_{21}H_{20}N_2O_4S$	39.00	140
24		OCH_3	S	$C_{20}H_{18}N_2O_3S$	48.00	190
25	H	OCH_3	S	$C_{14}H_{14}N_2O_3S$	40.50	150
26		OCH_3	S	$C_{21}H_{20}N_2O_4S$	50.50	164
27		OCH_3	S	$C_{20}H_{18}N_2O_4S$	40.00	200
28		OCH_3	S	$C_{20}H_{18}N_2O_4S$	51.47	165

$$pMIC = 4.95113 - 0.31731(\pm 0.1341)* PC+ - 0.02626 (\pm 0.0130)* Q\_VSA\_PNEG + 0.01250(\pm 0.0029)* SMR\_VSA7$$

$$n = 18,\ r^2 = 0.76165,\ q^2 = 0.584635,\ SE = 0.2258,\ F = 14.91,\ p = 0.0001 \qquad (2)$$

Table 2. Antibacterial activity of the title compounds (**1-28**) on *S. Aureus.*

Compound	Minimum inhibitory concentration (MIC) in µg/mL	pMIC
1	250	3.1636
2	62	3.8177
3	125	3.4991
4	1000	2.5916
5	500	2.8517
6	500	2.8813
7	250	3.1466
8	125	3.3413
9	500	2.8767
10	500	2.8342
11	500	2.8650
12	250	3.1263
13	62	3.6197
14	125	3.4799
15	32	4.0564
16	1000	2.5568
17	125	3.4154
18	500	2.8456

19	500	2.8813
20	62	3.6910
21	125	3.5164
22	500	2.8992
23	62	3.8058
24	32	4.0589
25	250	3.0650
26	62	3.8058
27	500	2.8836
28	62	3.7902

$$pMIC = 4.96716 - 0.32007(\pm 0.1361)* PC+ + 0.01163(\pm 0.0032)* SMR\_VSA7 - 0.70285(\pm 0.3643)* FCASA-$$

$$n = 18,\ r^2 = 0.75649,\ q^2 = 0.588355,\ SE = 0.2243,\ F = 14.50,\ p = 0.0001 \quad (3)$$

Table 3. Calculated molecular descriptors of the title compounds (**1-28**).

Compound	[A]PEOE_VSA_ PNEG	[B]PEOE_VSA_ PPOS	[C]PC+	[D]Q_VSA_ PNEG	[E]SMR_VSA7	[F]FCASA-
Training set						
1	43.3414	45.0986	4.8960	43.3414	66.6520	1.6270
2	43.3414	45.0986	5.5840	43.3414	132.4464	1.4232
3	45.8452	45.0986	5.1080	45.8452	102.0359	1.4768
4	43.3414	45.0986	5.2180	55.5963	66.6520	1.8380
5	43.3414	63.8813	5.3040	43.3414	66.6520	1.4479
6	51.1090	55.4227	5.2780	51.1090	66.6520	1.7826
7	43.3414	45.0986	4.8960	43.3414	68.7099	1.7299
8	43.3414	45.0986	4.0020	43.3414	68.7099	1.4326
9	43.3414	45.0986	5.2180	55.5963	68.7090	1.9344
10	43.3414	63.8813	5.3040	43.3414	68.7090	1.5176
11	51.1090	55.4227	5.2780	51.1090	68.7099	1.9028
12	40.8377	30.3901	4.4660	40.8377	66.6520	1.6847
13	40.8377	30.3901	3.5720	40.8377	66.6520	1.3479
14	40.8377	30.3901	5.1540	40.8377	132.4464	1.4465
15	43.3414	30.3901	4.6780	43.3414	102.0359	1.5140
16	40.8377	30.3901	4.7880	53.0926	66.6520	1.8762
17	40.8377	49.1728	4.8740	40.8377	66.6520	1.4325
18	48.6052	40.7142	4.8480	48.6052	66.6520	1.8224
Test set						
19	29.7745	27.6580	4.7060	0.1596	111.8441	1.7137
20	29.7745	27.6580	3.8120	0.1956	111.8441	1.3848
21	32.2782	27.6580	4.9180	0.1533	147.2279	1.5742
22	37.5420	37.9822	5.0880	0.1753	111.8441	1.8573
23	37.5420	37.9822	5.0880	0.1753	111.8441	1.8462
24	29.7745	27.6580	4.7060	0.1672	113.9019	1.8198
25	29.7745	27.6580	3.8120	0.2071	113.9019	1.4753
26	32.2782	27.6580	4.9180	0.1599	149.2858	1.6563
27	37.5420	37.9822	5.0880	0.1834	113.9019	1.9768
28	37.5420	37.9822	5.0880	0.1834	113.9019	1.9726

A: Total polar negative vdw surface area. B: Total polar positive vdw surface area. C: Total positive partial charge. D: Total polar negative vdw surface area. E: vdw surface area in molar refractivity (SMR). F: Fractional charge-weighed negative surface area.

$$pMIC = 4.35070 + 0.01201\ (\pm 0.0077)^{*}\ PEOE\_VSA\_PPOS - 0.63991\ (\pm 0.1704)^{*}\ PC+ + 0.01820(\pm 0.0033)^{*}\ SMR\_VSA7$$

$$n = 18,\ r^2 = 0.73685,\ q^2 = 0.553238,\ SE = 0.2373,\ F = 13.07,\ p = 0.0002 \quad (4)$$

Table 4. Correlation matrix.

	pMIC	PEOE_VSA_ PNEG	PEOE_ VSA_PPOS	PC+	Q_VSA_ PNEG	SMR_ VSA7	FCASA-
pMIC	1.0000						
PEOE_VSA_PNEG	-0.2753	1.0000					
PEOE_VSA_PPOS	-0.3750	0.4660	1.0000				
PC+	-0.2163	0.3324	0.4763	1.0000			
Q_VSA_PNEG	-0.5668	0.4457	0.1359	0.3277	1.0000		
SMR_VSA7	0.4055	-0.1111	-0.2380	0.4278	-0.2923	1.0000	
FCASA-	-0.5315	0.4305	0.0233	0.3333	0.8257	-0.3773	1.0000

Table 5. Observed, predicted pMIC and residual values for model – 2.

Compound	pMIC observed	pMIC predicted	Residuals
Training set			
1	3.1636	3.0926	0.0710
2	3.8177	3.6966	0.1211
3	3.4991	3.4018	0.0972
4	2.5916	2.6687	-0.0771
5	2.8517	2.9631	-0.1114
6	2.8813	2.7674	0.1138
7	3.1466	3.1183	0.0283
8	3.3413	3.4020	-0.0607
9	2.8767	2.6944	0.1823
10	2.8342	2.9889	-0.1546
11	2.8650	2.7932	0.0718
12	3.1263	3.2948	-0.1685
13	3.6197	3.5785	0.0412
14	3.4799	3.8988	-0.4188
15	4.0564	3.6040	0.4524
16	2.5568	2.8780	-0.3140
17	3.4154	3.1653	0.2501
18	2.8456	2.9696	-0.1241
Test set			
19	2.8813	3.2499	-0.3686
20	3.6910	3.5336	0.1574
21	3.5164	3.5591	-0.0427
22	2.8992	2.9247	-0.0255
23	3.8058	2.9247	0.8811
24	4.0589	3.2756	0.7833
25	3.0650	3.5593	0.4943
26	3.8058	3.5848	0.2210
27	2.8836	2.9504	-0.0668
28	3.7902	2.9504	0.8398

Out of the four models, model-2 was selected on the basis of statistical criteria; $r^2 = 0.76165$, SE = 0.2258, F = 14.91, p = 0.0001. The high q^2 in model-2 ($q^2 = 0.584635$) is indicative of its reliability in prediction of antibacterial activity in this series. The predictive ability was validated by predicting the antibacterial activity of test set which was excluded from the development of QSAR model. The low residual activity observed in case of training as well as test sets (Table 5) indicates the reliability of the selected QSAR model.

It is evident from the QSAR studies that in model-2, total positive partial charge (PC+) and total polar negative Van der Waals surface area (Q_VSA_PNEG) contributes negatively where as contribution of Van der Waals surface area to molar refractivity (SMR_VSA7) contributes positively to the antibacterial activity.

CONCLUSIONS

In 3-benzoyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine series the antibacterial activity is governed by total positive partial charge (PC+), total polar negative Van der Waals surface area (Q_VSA_PNEG) and contribution of Van der Waals surface area to molar refractivity (SMR_VSA7). The new molecules having less positive partial charge and polar negative Van der Waals surface area with higher contribution of Van der Waals surface area to molar refractivity may lead to improved antibacterial activity from this series.

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