Med Chem Res
DOI 10.1007/s00044-012-0189-5

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

In vitro anti-inflammatory potential and QSAR analysis of oxazolo/thiazolo pyrimidine derivatives

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Received: 24 January 2012 / Accepted: 4 August 2012

Abstract Twenty-six different benzylidene oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide derivatives were synthesized and evaluated for their anti-inflammatory potential by protein denaturation method. The structures of title compounds were characterized by IR and NMR spectral data. The SAR studies reveal that compounds containing electron withdrawing polar group at para position of 5-phenyl ring and electron withdrawing non-polar group at para position of 2-benzylidene moiety of thiazolo pyrimidine nucleus have better anti-inflammatory potential. The 2D-QSAR studies were performed on VLife MDS software which reveals that anti-inflammatory potential of benzylidene-3-oxo-5*H*-oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamides is dependent on estate contribution, alignment independent, individual and path count descriptors.

Keywords Anti-inflammatory potential · Oxazolopyrimidine · Thiazolopyrimidine · Carboxamide · 2D QSAR

Introduction

Pyrimidines possess versatile biological activities such as calcium channel modulator (Kappe, 1998; Sawant *et al*., 2011), selective 1-adrenoreceptor antagonist (Barrow *et al*., 2000), HIV gpl20-CD4 inhibitior (Patil *et al*., 1995), antiviral (Hurst and Hull, 1961), anticancer drug with mitotic kinesin inhibition (Kappe *et al*., 2000), oral antihypertensive (Kappe, 2000a, b), blood platelet aggregation inhibitor (Tozkoparan *et al*., 1995), drug for the treatment of benign prostatic hyperplasia (Nagarathnam *et al*., 1998), anti-inflammatory (Tozkoparan *et al*., 2000), muscarinic (Jung *et al*., 2001), antifungal, and antibacterial drugs (Kappe, 2000a, b; Sawant and Bhatia, 2009). Thiazolidinone derivatives are associated with diverse biological activities like antibacterial, antifungal, and antitubercular (Sharma *et al*., 2009). It is well known that pyrimidine and fused heterocyclic pyrimidine derivatives are of great biological interest, especially as antiviral, antitumor, antimicrobial, and anti-inflammatory agents (Mishra and Tomar, 2011; Wilson *et al*., 2008; Renslo *et al*., 2006; Ashok *et al*., 2007; Zaher and Elassar, 2002; Shah and Vaghasia, 2007).

Inflammation is the response of living tissues to injury. It involves a complex array of enzyme activation, mediator release, and extravasations of fluid, cell migration, tissue breakdown and repair (Chinnasamy *et al*., 2010; Mwangi *et al*., 2011). Many in vitro assays, each based on a specific biochemical or cellular mechanism have been developed for the initial screening of the anti-inflammatory compounds. A number of anti-inflammatory drugs are known to inhibit the denaturation of proteins as an in vitro screening model for anti-inflammatory compounds (Naik and Sheth, 1976).

The QSAR analysis infers the biological activity of new or untested chemical from the molecular structure, or properties of similar compounds whose activities have already been assessed (Schultz *et al*., 2003). 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

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Published online: 17 August 2012

new chemical compounds without the need to synthesize and test them (Sawant and Bhatia, 2008).

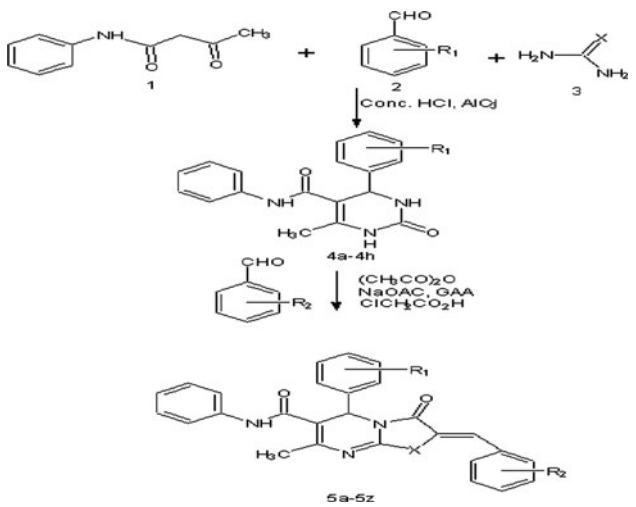
In the present work, we propose to synthesize a series of benzylidene-3-oxo-5*H*-oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamides, confirm their structures by spectral analysis, and evaluate the title compounds for their anti-inflammatory potential by protein denaturation method and 2D-QSAR analysis to deduce a correlation between structure and anti-inflammatory potential.

Experimental section

Twenty-six different benzylidene oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide derivatives (**5a**–**5z**) were synthesized according to Scheme 1. Melting points were determined using precision digital melting point apparatus VEEGO (Model-VMP-D) and are uncorrected. Completion of reaction was routinely checked by TLC using mobile phase as toluene: chloroform: ethyl acetate. The IR spectra were recorded on Jasco FT/IR 4100 spectrophotometer. ^{1}H NMR spectra were recorded on Varian Mercury YH-300 spectrometer using $CDCl_3$ as a solvent and TMS as internal standard. Chemical shifts are reported in ppm. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

General procedure for the synthesis (Pansuriya *et al*., 2009) of tetrahydropyrimidine-5-carboxamide (**4a**–**4h**)

A mixture of appropriate aromatic aldehyde (10 mmol); acetoacetanilide (10 mmol); and urea or thiourea (15 mmol) in methanol (25 ml) and concentrated hydrochloric acid (two drops); and aluminum chloride (3 mmol) was placed in round bottom flask. The mixture was heated to reflux for 7–8 h. The resulting solution was cooled to room temperature and poured into crushed ice with vigorous stirring. The resulting solid was filtered and washed with cold methanol.



Scheme 1 Synthesis of benzylidene oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide

General procedure for the synthesis (Alam *et al*., 2010) of benzylidene-3-oxo-5*H*-oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5a**–**5z**)

A mixture of tetrahydropyrimidine carboxamide derivative (10 mmol), monochloroacetic acid (15 mmol), anhydrous sodium acetate (2 g), glacial acetic acid (20 ml), acetic anhydride (15 ml), and aromatic aldehyde (10 mmol) were heated to reflux, and temperature was maintained at 140–142 °C for 4–5 h. The resulting solution was cooled to room temperature and poured the reaction mixture in ice water (150 ml) to yield solid product. Compound obtained was filtered and recrystallized from ethanol.

*2-(4-Methoxybenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5a**)*

Yield: 89.11 %. m.p. 196–197 °C. IR (KBr), v, cm^{-1}: 3371.93 (NH), 3055 (=C–H), 1712.94 (C=O), 1643.32 (C=O), 1593.42 (C=N), 1261.78 (Asy Ar–OCH_3), 1029.04 (Sym Ar–OCH_3), 701.56 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.56 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.13 (s, 1H, Ar–CH), 7.19–7.69 (m, 14H, Ar–CH), 7.42 (s, 1H, exocyclic CH), 7.92 (s, 1H, NH-amide).

*2-(4-Chlorobenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5b**)*

Yield: 73.87 %. m.p. 200–201 °C. IR (KBr), v, cm^{-1}: 3371.34 (NH), 3109.04 (=C–H), 1720.39 (C=O), 1643.24 (C=O), 1515.94 (C=N), 756.04 (C–Cl), 686.61 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.64 (s, 3H, CH_3), 5.41 (s, 1H, Ar–CH), 6.93–7.66 (m, 14H, Ar–CH), 7.41 (s, 1H, exocyclic CH), 8.18 (s, 1H, NH-amide).

*2-(4-Nitrobenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5c**)*

Yield: 68.44 %. m.p. 206–208 °C. IR (KBr), v, cm^{-1}: 3348.72 (NH), 3025.33 (=C–H), 1718.46 (C=O), 1658.32 (C=O), 1523.42 (C=N), 1499.43 (Asy Ar–NO_2), 1312.49 (Sym Ar–NO_2), 704.36 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.60 (s, 3H, CH_3), 5.84 (s, 1H, Ar–CH), 6.99–7.58 (m, 14H, Ar–CH), 7.44 (s, 1H, exocyclic CH), 7.96 (s, 1H, NH-amide).

*2-(4-Dimethylaminobenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5d**)*

Yield: 75.55 %. m.p. 186–188 °C. IR (KBr), v, cm^{-1}: 3328.53 (NH), 3043.67 (=C–H), 1708.23 (C=O), 1665.18 (C=O), 1606.22 (C=N), 1192.98 (C–N), 693.20 (C–S). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.59 (s, 3H, CH_3), 3.062 (s, 6H, $(CH_3)_2$), 5.64 (s, 1H, Ar–CH), 7.01–7.54 (m, 14H, Ar–CH), 7.47 (s, 1H, exocyclic CH), 7.94 (s, 1H, NH-amide).

*2-(4-Methoxybenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5e**)*

Yield: 80.68 %. m.p. 203–205 °C. IR (KBr), v, cm^{-1}: 3370.93 (NH), 3054 (=C–H), 1713.94 (C=O), 1665.32 (C=O),1596.42 (C=N), 1262.78 (Asy Ar–OCH_3), 1030.04 (Sym Ar–OCH_3), 1028.66 (C–O). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.55 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.09 (s, 1H, Ar–CH), 7.04–7.18 (m, 14H, Ar–CH), 7.45 (s, 1H, exocyclic CH), 8.02 (s, 1H, NH-amide).

*2-(4-Chlorobenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5f**)*

Yield: 86.30 %. m.p. 207–208 °C. IR (KBr), v, cm^{-1}: 3368.34 (NH), 3107.04 (=C–H), 1716.39 (C=O), 1659.24 (C=O), 1518.94 (C=N), 1018.44 (C–O), 758.04 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.62 (s, 3H, CH_3), 5.98 (s, 1H, Ar–CH), 6.99–7.33 (m, 14H, Ar–CH), 7.46 (s, 1H, exocyclic CH), 8.11 (s, 1H, NH-amide).

*2-(4-Nitrobenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5g**)*

Yield: 88.83 %. m.p. 210–211 °C. IR (KBr), v, cm^{-1}: 3346.72 (NH), 3045.33 (=C–H), 1716.46 (C=O), 1690.32 (C=O), 1574.42 (C=N), 1509.88 (Asy Ar–NO_2), 1322.49 (Sym Ar–NO_2), 1035.87 (C–O). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.57 (s, 3H, CH_3), 6.08 (s, 1H, Ar–CH), 6.94–7.21 (m, 14H, Ar–CH), 7.42 (s, 1H, exocyclic CH), 7.89 (s, 1H, NH-amide).

*2-(4-Dimethylaminobenzylidene)-7-methyl-3-oxo-N,5-diphenyl-2,3-dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5h**)*

Yield: 63.90 %. m.p. 189–191 °C. IR (KBr), v, cm^{-1}: 3330.53 (NH), 3043.67 (=C–H), 1703.25 (C=O), 1685.18 (C=O), 1609.22 (C=N), 1197.82 (C–N), 1065.35 (C–O). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.63 (s, 3H, CH_3), 3.04 (s, 6H, $(CH_3)_2$), 5.84 (s, 1H, Ar–CH), 7.02–7.65 (m, 14H, Ar–CH), 7.38 (s, 1H, exocyclic CH), 7.98 (s, 1H, NH-amide).

*5-(4-Methoxyphenyl)-N-phenyl-2-(4-chlorobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5i**)*

Yield: 78.63 %. m.p. 206–207 °C. IR (KBr), v, cm^{-1}: 3321.19 (NH), 3001.03 (=C–H), 1712.67 (C=O), 1647.10 (C=O),1512.09 (C=N), 1245.93 (Asy Ar–OCH_3), 1076.28 (Sym Ar–OCH_3), 756.04 (C–Cl), 694.33 (C–S). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.68 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.65 (s, 1H, Ar–CH), 6.96–7.56 (m, 13H, Ar–CH), 7.40 (s, 1H, exocyclic CH), 8.02 (s, 1H, NH-amide).

*5-(4-Methoxyphenyl)-N-phenyl-2-(4-nitrobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5j**)*

Yield: 80.78 %. m.p. 215–217 °C. IR (KBr), v, cm^{-1}: 3367.57 (NH), 3086.65 (=C–H), 1716.23 (C=O), 1675.23 (C=O),1576.52 (C=N), 1494.43 (Asy Ar–NO_2), 1370.49 (Sym Ar–NO_2), 1246.93 (Asy Ar–OCH_3), 1054.28 (Sym Ar–OCH_3), 690.23 (C–S). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.66 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.63 (s, 1H, Ar–CH), 6.94–7.58 (m, 13H, Ar–CH), 7.36 (s, 1H, exocyclic CH), 7.98 (s, 1H, NH-amide).

*5-(4-Methoxyphenyl)-N-phenyl-2-(4-dimethylamino-benzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5k**)*

Yield: 72.28 %. m.p. 198–200 °C. IR (KBr), v, cm^{-1}: 3332.59 (NH), 3090.42 (=C–H), 1707.84 (C=O), 1686.28 (C=O),1572.53 (C=N), 1244.93 (Asy Ar–OCH_3), 1046.28 (Sym Ar–OCH_3), 1189.78 (C–N), 692.66 (C–S). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.56 (s, 3H, CH_3), 3.06 (s, 6H, $(CH_3)_2$), 3.69 (s, 3H, OCH_3), 5.69 (s, 1H, Ar–CH), 6.92–7.52 (m, 13H, Ar–CH), 7.39 (s, 1H, exocyclic CH), 8.00 (s, 1H, NH-amide).

*5-(4-Methoxyphenyl)-N-phenyl2-(4-chlorobenzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5l**)*

Yield: 83.44 %. m.p. 213–214 °C. IR (KBr), v, cm^{-1}: 3368.57 (NH), 3088.65 (=C–H), 1716.23 (C=O), 1675.23 (C=O), 1596.52 (C=N), 1244.93 (Asy Ar–OCH_3), 1078.28 (Sym Ar–OCH_3), 1022.23 (C–O), 760.04 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$, TMS):δ 1.66 (s, 3H, CH_3), 3.79 (s, 3H,

OCH_3), 5.63 (s, 1H, Ar–CH), 6.95–7.57 (m, 13H, Ar–CH), 7.38 (s, 1H, exocyclic CH), 7.96 (s, 1H, NH-amide).

*5-(4-Methoxyphenyl)-N-phenyl-2-(4-nitrobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) oxazolo(3,2-a) pyrimidine-6-carboxamide (**5m**)*

Yield: 76.45 %. m.p. 220–222 °C. IR (KBr), v, cm^{-1}: 3330.59 (NH), 3059.42 (=C–H), 1705.84 (C=O), 1689.28 (C=O),1579.53 (C=N), 1493.88 (Asy Ar–NO_2), 1345.11 (Sym Ar–NO_2), 1251.93 (Asy Ar–OCH_3), 1072.28 (Sym Ar–OCH_3), 1023.18 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.61 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.66 (s, 1H, Ar–CH), 6.93–7.51 (m, 13H, Ar–CH), 7.40 (s, 1H, exocyclic CH), 7.99 (s, 1H, NH-amide).

*5-(4-Methoxyphenyl)-N-phenyl-2-(4-dimethyl-aminobenzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5n**)*

Yield: 85.32 %. m.p. 201–203 °C. IR (KBr), v, cm^{-1}: 3328.23 (NH), 3018.03 (=C–H), 1710.67 (C=O), 1661.10 (C=O), 1520.09 (C=N), 1255.39 (Asy Ar–OCH_3), 1076.28 (Sym Ar–OCH_3), 1190.75 (C–N), 1021.54 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.62 (s, 3H, CH_3), 3.05 (s, 6H, $(CH_3)_2$), 3.86 (s, 3H, OCH_3), 5.70 (s, 1H, Ar–CH), 6.92–7.56 (m, 13H, Ar–CH), 7.36 (s, 1H, exocyclic CH), 7.86 (s, 1H, NH-amide).

*5-(4-Chlorophenyl)-N-phenyl-2-(4-methoxybenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5o**)*

Yield: 77.33 %. m.p. 221–223 °C. IR (KBr), v, cm^{-1}: 3328.19 (NH), 3031.03 (=C–H), 1709.67 (C=O), 1679.10 (C=O), 1514.09 (C=N), 1245.93 (Asy Ar–OCH_3), 1076.28 (Sym Ar–OCH_3), 765.04 (C–Cl), 691.33 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.68 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.41 (s, 1H, Ar–CH), 6.82–7.23 (m, 13H, Ar–CH), 7.41 (s, 1H, exocyclic CH), 8.05 (s, 1H, NH-amide).

*5-(4-Chlorophenyl)-N-phenyl-2-(4-nitrobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5p**)*

Yield: 84.49 %. m.p. 225–226 °C. IR (KBr), v, cm^{-1}: 3322.19 (NH), 3011.03 (=C–H), 1703.67 (C=O), 1682.10 (C=O),1510.09 (C=N), 1496.43 (Asy Ar–NO_2), 1343.49 (Sym Ar–NO_2), 757.06 (C–Cl), 697.23 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.67 (s, 3H, CH_3), 5.39 (s, 1H, Ar–CH), 6.86–7.51 (m, 13H, Ar–CH), 7.43 (s, 1H, exocyclic CH), 7.86 (s, 1H, NH-amide).

*5-(4-Chlorophenyl)-N-phenyl-2-(4-dimethyl-aminobenzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5q**)*

Yield: 76.22 %. m.p. 216–218 °C. IR (KBr), v, cm^{-1}: 3326.53 (NH), 3016.52 (=C–H), 1695.32 (C=O), 1665.23 (C=O), 1573.52 (C=N), 1190.78 (C–N), 751.06 (C–Cl), 702.65 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.63 (s, 3H, CH_3), 3.34 (s, 6H, $(CH_3)_2$), 5.37 (s, 1H, Ar–CH), 6.91–7.76 (m, 13H, Ar–CH), 7.35 (s, 1H, exocyclic CH), 8.12 (s, 1H, NH-amide).

*5-(4-Chlorophenyl)-N-phenyl-2-(4-dimethyl-aminobenzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5r**)*

Yield: 87.37 %. m.p. 220–222 °C. IR (KBr), v, cm^{-1}: 3328.25 (NH), 3057.03 (=C–H), 1709.67 (C=O), 1658.10 (C=O),1514.09 (C=N), 1245.93 (Asy Ar–OCH_3), 1056.28 (Sym Ar–OCH_3), 1016.23 (C–O), 756.04 (C–Cl). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.65 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.35 (s, 1H, Ar–CH), 6.93–7.32 (m, 13H, Ar–CH), 7.45 (s, 1H, exocyclic CH), 7.92 (s, 1H, NH-amide).

*5-(4-Chlorophenyl)-N-phenyl-2-(4-nitrobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5s**)*

Yield: 80.65 %. m.p. 226–228 °C. IR (KBr), v, cm^{-1}: 3322.26 (NH), 3011.03 (=C–H), 1706.67 (C=O), 1662.10 (C=O),1510.09 (C=N), 1532.28 (Asy Ar–NO_2), 1313.45 (Sym Ar–NO_2), 757.06 (C–Cl), 1022.98 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.64 (s, 3H, CH_3), 6.12 (s, 1H, Ar–CH), 6.95–7.84 (m, 13H, Ar–CH), 7.44 (s, 1H, exocyclic CH), 8.16 (s, 1H, NH-amide).

*5-(4-Chlorophenyl)-N-phenyl-2-(4-dimethylaminobenzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5t**)*

Yield: 75.29 %. m.p. 219–220 °C. IR (KBr), v, cm^{-1}: 3278.76 (NH), 3035.75 (=C–H), 1701.10 (C=O), 1643.24 (C=O),1585.38 (C=N), 1195.78 (C–N), 744.47 (C–Cl), 1014.22 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.58 (s, 3H, CH_3), 3.06 (s, 6H, $(CH_3)_2$), 5.34 (s, 1H, Ar–CH), 6.93–7.68 (m, 13H, Ar–CH), 7.38 (s, 1H, exocyclic CH), 8.22 (s, 1H, NH-amide).

*5-(4-Nitrophenyl)-N-phenyl-2-(4-methoxybenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5u**)*

Yield: 81.60 %. m.p. 227–228 °C. IR (KBr), v, cm^{-1}: 3324.53 (NH), 3076.52 (=C–H), 1718.23 (C=O), 1669.23

(C=O), 1570.52 (C=N), 1494.76 (Asy Ar–NO_2), 1345.11 (Sym Ar–NO_2), 1248.54 (Asy Ar–OCH_3), 1042.11 (Sym Ar–OCH_3), 700.86 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.68 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 5.96 (s, 1H, Ar–CH), 6.96–7.25 (m, 13H, Ar–CH), 7.46 (s, 1H, exocyclic CH), 8.01 (s, 1H, NH-amide).

*5-(4-Nitrophenyl)-N-phenyl-2-(4-chlorobenzylidene)-7-methyl-3-oxo-2,3 dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5v**)*

Yield: 72.66 %. m.p. 230–231 °C. IR (KBr), v, cm^{-1}: 3316.53 (NH), 3065.18 (=C–H), 1693.23 (C=O), 1671.23 (C=O), 1579.52 (C=N), 1493.88 (Asy Ar–NO_2), 1345.11 (Sym Ar–NO_2), 755.21 (C–Cl), 695.65 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.65 (s, 3H, CH_3), 6.03 (s, 1H, Ar–CH), 6.84–7.14 (m, 13H, Ar–CH), 7.45 (s, 1H, exocyclic CH), 8.04 (s, 1H, NH-amide).

*5-(4-Nitrophenyl)-N-phenyl-2-(4-dimethyl-aminobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) thiazolo (3,2-a)-pyrimidine-6-carboxamide (**5w**)*

Yield: 79.25 %. m.p. 223–225 °C. IR (KBr), v, cm^{-1}: 3315.53 (NH), 3070.88 (=C–H), 1698.23 (C=O), 1667.23 (C=O), 1575.62 (C=N), 1499.93 (Asy Ar–NO_2), 1335.11 (Sym Ar–NO_2), 1197.87 (C–N), 693.73 (C–S). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.63 (s, 3H, CH_3), 3.24 (s, 6H, $(CH_3)_2$), 5.94 (s, 1H, Ar–CH), 6.93–7.84 (m, 13H, Ar–CH), 7.42 (s, 1H, exocyclic CH), 7.96 (s, 1H, NH-amide).

*5-(4-Nitrophenyl)-N-phenyl-2-(4-methoxybenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5x**)*

Yield: 86.06 %. m.p. 230–232 °C. IR (KBr), v, cm^{-1}: 3298.05 (NH), 3016.46 (=C–H), 1708.81 (C=O), 1674.10 (C=O), 1573.81 (Asy Ar–NO_2), 1342.36 (Sym Ar–NO_2), 1257.50 (Asy Ar–OCH_3), 1064.63 (Sym Ar–OCH_3), 1515.94 (C=N), 1029.92 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.58 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.99 (s, 1H, Ar–CH), 7.23–7.66 (m, 13H, Ar–CH), 7.41 (s, 1H, exocyclic CH), 7.99 (s, 1H, NH-amide).

*5-(4-Nitrophenyl)-N-phenyl-2-(4-chlorobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5y**)*

Yield: 78.62 %. m.p. 235–236 °C. IR (KBr), v, cm^{-1}: 3299.53 (NH), 3045.18 (=C–H), 1698.28 (C=O), 1672.23 (C=O), 1579.59 (C=N), 1566.78 (Asy Ar–NO_2), 1344.11 (Sym Ar–NO_2), 1028.65 (C–O–C), 753.21 (C–Cl). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.54 (s, 3H, CH_3), 5.92 (s, 1H, Ar–CH), 6.23–7.26 (m, 13H, Ar–CH), 7.40 (s, 1H, exocyclic CH), 8.04 (s, 1H, NH-amide).

*5-(4-Nitrophenyl)-N-phenyl-2-(4-dimethyl-aminobenzylidene)-7-methyl-3-oxo-2,3dihydro-5H (1,3) oxazolo (3,2-a)-pyrimidine-6-carboxamide (**5z**)*

Yield: 65.16 %. m.p. 231–233 °C; IR (KBr), v, cm^{-1}: 3349.57 (NH), 3072.88 (=C–H), 1704.23 (C=O), 1676.28 (C=O), 1579.62 (C=N), 1508.43 (Asy Ar–NO_2), 1345.11 (Sym Ar–NO_2), 1191.78 (C–N), 1018.65 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$, TMS):δ 1.56 (s, 3H, CH_3), 3.16 (s, 6H, $(CH_3)_2$), 6.00 (s, 1H, Ar–CH), 6.36–7.09 (m, 13H, Ar–CH), 7.38 (s, 1H, exocyclic CH), 7.92 (s, 1H, NH-amide).

Anti-inflammatory potential

The title compounds were screened for anti-inflammatory potential by inhibition of albumin denaturation technique (Singh *et al*., 2009; Sakat *et al*., 2010). The standard drug and test compounds were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0 %. Test solution (1 ml) containing different concentration of compounds were mixed with 1 ml of 1 % mM albumin solution in phosphate buffer and incubated at 27 ± 1 °C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60 ± 1 °C in water bath for 10 min. After cooling the turbidity was measured at 660 nm. Percentage inhibition of denaturation was calculated from control. Each experiment was performed in triplicate and average was taken. The diclofenac sodium was used as standard drug. Percentage inhibition was calculated using formula

$$\% \text{ inhibition} = 100 \times (1 - (\text{Vt}/\text{Vc}))$$

where, Vt and Vc are mean absorbance value of test group and control group, respectively. From percentage inhibition, the half maximal inhibitory concentration (IC_{50}) was calculated.

QSAR analysis

Dataset

The builder module of the VLife MDS was used to generate molecular models of series of benzylidene-3-oxo-5*H*-oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide derivatives. The structures were then energy minimized using the Merck molecular force field (MMFF). The biological activity values for the QSAR equation were obtained using the negative logarithm of half maximal inhibitory concentration.

Activity prediction

The predictability of the QSAR model would be good if the values of biological activity predicted by the QSAR model do not appreciably differ from the observed results of biological activity for the given dataset.

Computational details

The structures were sketched using 2D Draw App and were exported to QSAR Plus through MDS path. Three-dimensional structures of all the molecules were generated. For 2D QSAR, we used optimized molecule in 2D sheet and added pIC_{50} value. All the 2D calculated descriptors were considered as independent variables and pIC_{50} was considered as dependent variable. The training set and test set were selected using random selection method. Stepwise multiple linear regression analysis method and simulated annealing method were 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), cross-validated square correlation coefficient (q^2), and sequential Fischer test (F).

Results and discussion

The tetrahydropyrimidine-5-carboxamide derivatives **(4a–4h)** were synthesized by a three-component reaction involving acetoacetanilide (1), substituted benzaldehydes (2), and urea or thiourea (3) in the presence of concentrated hydrochloric acid and aluminum chloride as catalyst. Subsequently, tetrahydropyrimidine-5-carboxamides **(4a–4h)** were treated with chloroacetic acid, anhydrous sodium acetate, and substituted benzaldehydes in a mixture of acetic acid and acetic anhydride to afford the title compounds benzylidene-3-oxo-5*H*-oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide **(5a–5z)** as shown in Scheme 1 and Table 1. The purity of compounds was checked by thin layer chromatography. Their structures were confirmed by elemental analysis, and IR and ^{1}H NMR spectral studies. The amount of carbon, hydrogen, and nitrogen found by

Table 1 Chemical structures and physicochemical characteristics of title compounds (**5a–5z**)

Compound	X	R_1	R_2	Molecular formula	Melting point (°C)	% yield	R_f value
5a	S	H	4-OCH_3	$C_{28}H_{23}N_3O_3S$	196–197	89.11	0.74
5b	S	H	4-Cl	$C_{27}H_{20}N_3O_2SCl$	200–201	73.87	0.69
5c	S	H	4-NO_2	$C_{27}H_{20}N_4O_4S$	206–208	68.44	0.67
5d	S	H	4-$N(CH_3)_2$	$C_{29}H_{26}N_4O_2S$	186–188	75.55	0.76
5e	O	H	4-OCH_3	$C_{28}H_{23}N_3O_4$	203–205	80.68	0.72
5f	O	H	4-Cl	$C_{27}H_{20}N_3O_3Cl$	207–208	86.30	0.68
5g	O	H	4-NO_2	$C_{27}H_{20}N_4O_5$	210–211	88.83	0.64
5h	O	H	4-$N(CH_3)_2$	$C_{29}H_{26}N_4O_3$	189–191	63.90	0.75
5i	S	4-OCH_3	4-Cl	$C_{28}H_{22}N_3O_2SCl$	206–207	78.63	0.54
5j	S	4-OCH_3	4-NO_2	$C_{28}H_{22}N_4O_4S$	215–217	80.78	0.51
5k	S	4-OCH_3	4-$N(CH_3)_2$	$C_{30}H_{28}N_4O_3S$	198–200	72.28	0.65
5l	O	4-OCH_3	4-Cl	$C_{28}H_{22}N_3O_3Cl$	213–214	83.44	0.52
5m	O	4-OCH_3	4-NO_2	$C_{28}H_{22}N_4O_5$	220–222	76.45	0.50
5n	O	4-OCH_3	4-$N(CH_3)_2$	$C_{30}H_{28}N_4O_4$	201–203	85.32	0.65
5o	S	4-Cl	4-OCH_3	$C_{28}H_{22}ClN_3O_3S$	221–223	77.33	0.53
5p	S	4-Cl	4-NO_2	$C_{27}H_{19}ClN_4O_4S$	225–226	84.49	0.50
5q	S	4-Cl	4-$N(CH_3)_2$	$C_{29}H_{25}ClN_4O_2S$	216–218	76.22	0.57
5r	O	4-Cl	4-OCH_3	$C_{28}H_{22}ClN_3O_4$	220–222	87.37	0.50
5s	O	4-Cl	4-NO_2	$C_{27}H_{19}ClN_4O_5$	226–228	80.65	0.49
5t	O	4-Cl	4-$N(CH_3)_2$	$C_{29}H_{25}ClN_4O_3$	219–220	75.29	0.56
5u	S	4-NO_2	4-OCH_3	$C_{28}H_{22}N_4O_5S$	227–229	81.60	0.49
5v	S	4-NO_2	4-Cl	$C_{27}H_{19}N_4O_4SCl$	230–231	72.66	0.44
5w	S	4-NO_2	4-$N(CH_3)_2$	$C_{29}H_{25}N_5O_4S$	223–225	79.25	0.59
5x	O	4-NO_2	4-OCH_3	$C_{28}H_{22}N_4O_6$	230–232	86.06	0.48
5y	O	4-NO_2	4-Cl	$C_{27}H_{19}N_4O_5$	235–236	78.62	0.42
5z	O	4-NO_2	4-$N(CH_3)_2$	$C_{29}H_{25}N_5O_5$	231–233	65.16	0.59

Table 2 IC_{50} values for anti-inflammatory potential of title compounds (**5a–5z**)

Compound	IC_{50} (ppm)	Compound	IC_{50} (ppm)
Diclofenac	188.24		
5a	291.257	**5n**	314.544
5b	226.318	**5o**	232.597
5c	253.376	**5p**	190.42
5d	316.686	**5q**	309.862
5e	304.179	**5r**	242.144
5f	261.464	**5s**	192.486
5g	283.525	**5t**	319.524
5h	330.312	**5u**	250.38
5i	210.874	**5v**	194.611
5j	254.99	**5w**	336.75
5k	301.677	**5x**	259.104
5l	236.954	**5y**	196.05
5m	272.584	**5z**	339.35

elemental analysis is in good agreement with the calculated amount.

The anti-inflammatory drugs that are known to inhibit the heat-induced denaturation of proteins are used as in vitro screening model for anti-inflammatory compounds. Denaturation of protein is one of the well-documented cause of rheumatoid arthritis. Production of auto-antigen in certain arthritic disease may due to denaturation of protein. The mechanism of denaturation probably involves alteration of electrostatic hydrogen, hydrophobic, and disulfide bonding. The anti-inflammatory potential of benzylidene-3-oxo-5*H*-oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamides (**5a–5z**) was estimated as a ability to inhibit albumin denaturation and expressed as IC_{50} values (Table 2). The biological activity data (IC_{50}) was converted to negative log dose in moles (pIC_{50}) for QSAR analysis. The selected molecular descriptors of title compounds (**5a–5z**) are shown in Table 3. The best model was selected on the basis of various statistical parameters such as squared correlation coefficient (r^2), cross-validated square correlation coefficient (q^2), and sequential Fischer test (F).

2D QSAR

$pIC_{50} = 1.1384 + 0.0334$ (± 0.0500) SaaCHE index-0.0150 (± 0.2329) T_T_O_4-0.1717 (± 0.0043) slogp + 0.0271 (± 0.5106) 2Path Count (Model-1)

$n = 20$, $r^2 = 0.88$, $q^2 = 0.80$, F test = 37.8492.

The anti-inflammatory potential according to QSAR Model-1 is dependent on alignment independent (AI), estate contribution, individual and path count descriptors.

Table 3 Selected molecular descriptors of title compounds (**5a–5z**)

Comp no.	SaaCHE index	T_T_O_4	slogp	2Path Count
5a*	26.717163	11	5.3107	55
5b	27.575033	10	5.9555	54
5c	24.821455	14	5.2103	57
5d	27.314477	10	5.3681	57
5e	25.860158	16	4.5941	55
5f*	26.718028	15	5.2389	54
5g	23.96445	19	4.4937	57
5h	26.457472	15	4.6515	57
5i	25.283111	11	5.9641	57
5j*	22.577315	15	5.2189	60
5k	25.025893	11	5.3767	60
5l	24.470666	16	5.2475	57
5m	21.76487	20	4.5023	60
5n	24.213448	16	4.6601	60
5o	25.317953	11	5.9641	57
5p	23.459037	14	5.8637	59
5q*	25.907614	10	6.0215	59
5r*	24.505509	16	5.2475	57
5s	22.646592	19	5.1471	59
5t	25.095169	15	5.3049	59
5u	22.471516	15	5.2189	60
5v	23.318395	14	5.8637	59
5w	23.061177	14	5.2763	62
5x	21.659071	20	4.5023	60
5y	22.50595	19	5.1471	59
5z*	22.248732	19	4.5597	62

* Test set

For calculation of AI descriptors, every atom in the molecule was assigned at least one and at most three attributes. The first attribute is T attribute to thoroughly characterize the topology of the molecule. The second attribute is the atom type. The atom symbol is used here. The third attribute is assigned to atoms taking part in a double or triple bond. After all atoms have been assigned their respective attributes, selective distance count statistics for all combinations of different attributes were computed.

Model-1 reveals that descriptor T_T_O_4 is a negative contributor to activity which indicates the count of number of any atoms (single, double, or triple bonded) separated from any other oxygen atom (single, double, or triple bonded) by four bonds in a molecule. SaaCHE index is a positive contributor to activity which indicates electrotopological state indices for number of –CH group connected with two aromatic bonds. The slogp and 2Path Count will determine the activity. The slogp is negative contributor to activity. This descriptor signifies log of the octanol/water partition coefficient. This property calculates logP from the

given structure. The 2Path Count is a positive contributor to activity which indicates total number of fragments of second order (two bond path). Figure 1 shows contribution of selected descriptors to activity. The selected model 1 is predictive as observed and predicted pIC_{50} values are close with minimum residuals (Table 4).

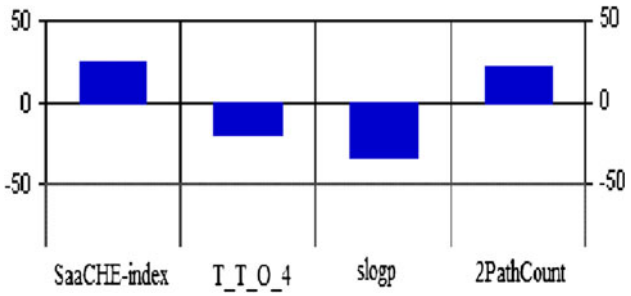


Fig. 1 Contribution chart of descriptors

Table 4 Observed, predicted, and residual pIC_{50} values for model 1

Compound	Observed	Predicted	Residual
5a*	2.445034	2.464276	0.01
5b	2.350788	2.354719	0.00
5c	2.408372	2.403765	0.00
5d	2.524331	2.500629	−0.02
5e	2.464616	2.483129	0.01
5f*	2.370370	2.417412	0.04
5g	2.427954	2.452591	0.02
5h	2.543913	2.518924	−0.02
5i	2.339269	2.324023	−0.01
5j*	2.398447	2.406523	0.00
5k	2.512923	2.479542	−0.03
5l	2.360337	2.374664	0.01
5m	2.419515	2.435500	0.01
5n	2.533991	2.497681	−0.03
5o	2.340431	2.366604	0.02
5p	2.304996	2.279713	−0.02
5q*	2.419472	2.491168	0.07
5r*	2.361499	2.384074	0.02
5s	2.326065	2.284399	−0.04
5t	2.440540	2.504503	0.06
5u	2.394918	2.398600	0.00
5v	2.300305	2.289167	−0.01
5w	2.473959	2.527308	0.05
5x	2.415986	2.413474	0.00
5y	2.321373	2.292367	−0.02
5z*	2.495028	2.530648	0.03

* Test set

Conclusion

A series of benzylidene oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamides were synthesized in good yields. The benzylidene thiazolo (3,2-a)-pyrimidine-6-carboxamide analogs have better anti-inflammatory potential than the benzylidene oxazolo (3,2-a)-pyrimidine-6-carboxamides. Inhibition of protein denaturation by the title compounds and subsequent QSAR analysis reveals that electron withdrawing polar group at para position of 5-phenyl ring and electron withdrawing non-polar group at para position of 2-benzylidene moiety of thiazolo pyrimidine nucleus improves anti-inflammatory potential in the series. This study forms the basis for the further design and synthesis of benzylidene oxazolo/thiazolo (3,2-a)-pyrimidine-6-carboxamide analogs as anti-inflammatory agent.

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