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Ionic-liquid mediated one-pot synthesis of novel thiazolidinones containing pyrazole and thiazole hybrid as COX-1/COX-2 inhibitor

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Abstract: A one-pot, ionic-liquid mediated synthesis has been developed for novel thiazolidine-4-ones containing a pyrazole and thiazole hybrid. This was achieved using a three-component reaction of 2-amino-thiazole, pyrazole-3-aldehyde, and mercaptoacetic acid in [bmim][PF6]. The whole procedure is robust and straightforward. By employing this protocol, a series of novel thiazolidine-4-ones containing pyrazole and thiazole hybrids were prepared in good yield (56-88%) and their preliminary cyclooxygenase activities were also studied and reported. The compounds **3h** and **3k** show the top-tier selective index for cyclooxygenase enzyme, in comparable with celecoxib as a standard.

Keywords: Ionic liquid; thiazoline-4-one; COX-1/COX-2; molecular docking.

1. Introduction

The nonsteroidal anti-inflammatory drugs (NSAIDs) are the class of FDA-approved drug used for the antipyretic, anti-inflammatory, and analgesic activities.[1] The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). The two distinct COX isoforms have been characterized as COX-1 and COX-2; COX-1 gets constitutively expressed in the body, and it plays important role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation. However, COX-2 is not constitutively expressed in the body; instead, it inducible expresses during an inflammatory response. Most of the NSAIDs are non-selective and inhibited both COX-1 and COX-2 having the same catalytic mechanism.[2] The main domain of these isomers contains fatty acid oxygenase and peroxidase active sites. COX-1 is a housekeeping enzyme which is responsible for the production of prostanoid in many tissues whilst COX-2 being an inducible enzyme,

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mainly expressed at the site of infection, inflammation and cancer, produces prostanoid which is responsible for disease pathogenesis.[3,4] Notably, the volume of COX-1 oxygenase site is about 20% smaller than that of COX-2.[5] Additionally, the COX-1 oxygenase site contains hydrophobic side-pocket in the proximity of Phe518.[6] Although, constitutive expression of COX-2 in brain, thymus and gastrointestinal tract without any significance inflammation plays a major role in development, maintenance and homeostatic function of the mentioned organs. It was observed that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin, ibuprofen and naproxen associated with several side effects such as gastrointestinal ulceration, bleeding and nephrotoxicity. These undesirable side effects are due to inhibition of COX-l enzyme. This isoform is involved in the physiological production of prostaglandins (PGs) that are responsible for maintaining gastric and renal integrity.[7] Therefore, development of COX-1/COX-2 inhibitor as nonsteroidal anti-inflammatory drug likewise activity is highly desirable.

The use of eco-friendly catalysts and solvents pertinent to organic and medicinal chemistry constitutes a domain of significant relevance. Considering both economic and environmental perspectives, the incorporation of non-volatile solvents and green catalysts is incredibly promising. Ionic liquids represent a distinguished category of organic salts that exist in a liquid phase at ostensibly reduced temperatures (below 100 °C), typically comprising an organic cation with either organic or inorganic anions.[8,9] Most of the cations and anions demonstrate an inert characteristic nature both at ambient temperature and under elevated temperature conditions. Owing to their polar nature, these species are recognized for their ability to dissolve the diverse array of organic compounds, gaseous molecules, organometallic complexes, and metallic salts, and these attributes render them effective solvents, particularly advantageous for organic synthesis.[10]

Thiazolidin-4-one is the saturated form of thiazole and their derivatives plays an important role in organic and medicinal chemistry which possess almost all types of biological activities such as antimicrobial,[11] anti-tubercular,[12] antifungal,[13] anti-diarrheal,[14] anticonvulsant,[15] Ca^{2+} channel blocker,[16] analgesic[17] and antioxidant[18] activities. In order to achieve significant biological activities, many researchers have attempted the synthesis of thiazolidin-4-one from a schiff base which received much more attention. Ionic liquid paved a significant attention for the synthesis of biological active thiazolidin-4-one due to its characteristics properties such as low vapour pressure, high thermal stability and low volatility.[19] Sadeghzadeh et *al*. synthesized substituted thiazolidin-4-ones using the concept of supported ionic liquid phase catalysis.[20] Mamaghani and his co-workers developed the route for substituted thiazolidinones using solid basic catalyst immobilized onto supported ionic liquid-like phase (SILLP).[21] A robust one-pot method has been reported for the synthesis of various heterocyclic bioactive substituted thiazolidin-4-ones by using ionic liquids.[22,23,24]

To careful survey of the literature, it was shown that thiazolidine-4-one scaffold plays a significant role against COX-1/COX-2 enzyme. Vasincu *et al.* studied the evaluation of ibuprofen derivatives with thiazolidine-4-one scaffold for their anti-inflammatory and analgesic activities.[25] It was found that the synthesized thiazolidine-4-one compounds were found to be less toxic than the reference drug; ibuprofen. Omar *et al.* evaluated the thiazolidin-4-ones for COX-1/COX-2 enzyme and concluded that the presence of aryl ring at 2-position of thiazolidin-4-ones is responsible to increase the COX-1/COX-2 inhibition activity.[26] Celeoxib and atipyrine are two established drugs containing pyrazole scaffold. After celecoxib, pyrazole has received considerable attention for the development of safer anti-inflammatory molecules.[27] Including, thiazole plays a significant role for inhibition of COX-1 and COX-2 enzyme. Considering the diversified applications of thiazolidin-4-ones toward different biological activity,[28] herein we explored the one-pot three component synthesis of novel 2-pyrazole-*N*-thiazole-thiazolidin-4-ones hybrid in ionic liquid and studied their biological activity against cyclooxygenase enzyme.

2. Experimental

2.1. Chemical Material and Apparatus

All new compounds were fully characterized. NMR experiments were performed with 500 MHz spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference.

J values are given in hertz. The ^{1}H and ^{13}C NMR spectra are referenced to the residual solvent signals (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C in $CDCl_3$, 2.50 ppm for ^{1}H and 39.9 ppm for ^{13}C in DMSO-d_6). IR spectra were recorded by using KBr pellets or neat. TOF and quadruple mass analyzer types were used for the HRMS measurements. Column chromatography was performed on silica gel (100−200 mesh) in glass columns to purify the compounds and visualized with UV light (254 nm), PMA and DNP stain. Commercially available reagents and solvents were used without further purification and were purchased. Melting points were determined using open capillary tubes and are uncorrected.

*2.2. General Procedure for the Synthesis of 2-pyrazole-N-thiazole-thiazolidinone (**3**)*

An equimolar mixture of 2-amino-thiazole **1** (25 mmol) and pyrazole-3-aldehyde **2** (25 mmol) was dissolved in an ionic liquid [Bmin][PF_6] (4 g), and the solution was stirred for 1 h at 120 °C. Thereafter, mercaptoacetic acid (37.5 mmol) was added, and the reaction content was allowed to stir at 120 °C for 1 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). The solid product was extracted by solvent extraction using ethyl acetate (25x2) and washed with 10% sodium bicarbonate (25x3). Evaporated organic solvent under vacuum and crude solid product was purified by column chromatography using eluent 5 to 15% ethyl acetate in petroleum ether to obtained pure thiazolidin-4-one (**3a-n**).

*2-(1,3-Diphenyl-N-pyrazol-4-yl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one (**3a**)*:Yellow solid; 206 mg; Yield 76%; mp: 165-173℃; IR (ν cm^{-1}) = 3020 (w), 2926 (w), 1682 (s), 1588 (w), 1501 (s), 1219 (s), 762 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.90 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 7.1 Hz, 2H), 7.72 (s, 1H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 3H), 7.50 - 7.44 (m, 2H), 7.31 - 7.21 (m, 4H), 6.89 (s, 1H), 4.44 (d, *J* = 15.9 Hz, 1H), 4.08 (d, J = 16.2 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.7, 156.2, 150.4, 148.9, 139.5, 133.9, 132.8, 129.9, 129.3, 128.9, 128.6, 128.3, 127.4, 126.9, 126.0, 123.3, 118.6, 109.5, 55.9, 33.8; GCMS for $C_{27}H_{20}N_4OS_2$ (*m/z*) = 480.1.

*2-(3-(4-Fluorophenyl)-N-phenyl-pyrazol-4-yl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one (**3b**)*: Yellow solid; 105 mg; Yield 86%; mp: 150-156 ℃; IR (ν cm^{-1}) = 3032 (w), 2916 (w), 1682 (s), 1598 (w), 1504 (s), 1219 (s), 760 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.89 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.81 - 7.76 (m, 2H), 7.72 (s, 1H), 7.53 (d, *J* = 6.7 Hz, 2H), 7.46 (dd, J_1 = 9 Hz, J_2 = 8.7 Hz 4H), 7.33 - 7.23 (m, 4H), 6.88 (s, 1H), 4.45 (d, *J* = 16.2 Hz, 1H), 4.07 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.7, 156.2, 150.4, 148.9, 139.5, 133.9, 132.8, 129.9, 129.3, 128.9, 128.6, 128.3, 127.4, 126.9, 126.0, 123.3, 118.6, 109.5, 55.9, 33.8; GCMS for $C_{27}H_{19}FN_4OS_2$ (*m/z*) = 498.0.

*2-(3-(4-Chlorophenyl)-N-phenyl-pyrazol-4-yl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one (**3c**)*: Brown solid; 105 mg; Yield 88%; mp: 149-155℃; IR (ν cm^{-1}) = 3025 (w), 2925 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 778 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.52 - 7.44 (m, 4H), 7.33 - 7.24 (m, 4H), 6.90 (s, 1H), 4.48 (d, *J* = 16.2 Hz, 1H), 4.08 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.7, 156.2, 150.4, 148.9, 139.5, 133.9, 132.8, 129.9, 129.3, 128.9, 128.6, 128.3, 127.4, 126.9, 126.0, 123.3, 118.6, 109.5, 55.9, 33.8; GCMS for $C_{27}H_{19}ClN_4OS_2$ (*m/z*) = 514.0.

*2-(3-(4-Methylphenyl)-N-phenyl-pyrazol-4-yl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one (**3d**)*: Yellow solid; 200 mg; Yield 79%; mp: 148-154 ℃; IR (ν cm^{-1}) = 3020 (w), 2926 (w), 1682 (s), 1598 (w), 1504 (s), 1219 (s), 762 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.86 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.72 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.56 (dd, J_1 = 7.8 Hz, J_2 =1.7 Hz, 2H), 7.48 - 7.40 (m, 4H), 7.31 - 7.24 (m, 4H), 6.88 (s, 1H), 4.44 (d, *J* = 16.1 Hz, 1H), 4.07 (d, *J* = 16.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.7, 156.1, 150.4, 148.7, 139.6, 138.3, 134.0, 129.9, 129.6, 129.0, 128.5, 128.4, 127.3, 126.9, 126.1, 123.3, 119.6, 118.6, 56.0, 32.5, 21.4; GCMS for $C_{28}H_{22}N_4OS_2$ (*m/z*) = 494.1.

*2-(1,3-diphenyl-N-pyrazol-4-yl)-3-(4-(p-tolyl)thiazol-2-yl)thiazolidin-4-one (**3e**)*: Yellow solid; 220 mg; Yield 56%; mp: 178-185℃; IR (ν cm^{-1}) = 3035 (w), 2900 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 768 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.63 (m, 3H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.50 - 7.41 (m, 4H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 4.43 (d, *J* = 16.2 Hz, 1H), 4.06 (d, *J* = 16.2 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.6, 156.2, 150.4, 149.0, 139.6, 137.7, 132.8, 131.3, 129.9, 129.6, 129.4, 128.6, 127.4, 127.0 126.0, 123.4, 118.6, 106.6, 56.0, 33.8, 21.2; GCMS for $C_{28}H_{28}N_4OS_2$ (*m/z*) = 494.1.

*2-(3-(4-Fluorophenyl)-N-phenyl--pyrazol-4-yl)-3-(4-(p-tolyl)thiazol-2-yl)thiazolidin-4-one (**3f**)*: Yellow solid; 138 mg; Yield 61%; mp: 168-175℃; IR (ν cm^{-1}) = 3025 (w), 2925 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 778 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.88 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.80 - 7.77 (m, 2H), 7.64 (s, 1H), 7.47 -7.42 (m, 6H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 1H), 4.44 (d, *J* = 16.1 Hz, 1H), 4.07 (d, *J* = 16.2 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.5, 156.2, 149.4, 149.0, 139.5, 137.8, 131.3, 130.8, 130.7, 129.9, 129.6, 127.5, 127.0, 126.0, 123.3, 118.7, 116.5, 116.3, 108.7, 55.9, 33.7, 21.2; GCMS for $C_{28}H_{21}FN_4OS_2$ (*m/z*) = 512.1.

*2-(3-(4-Methylphenyl)-N-phenyl--pyrazol-4-yl)-3-(4-(p-tolyl)thiazol-2-yl)thiazolidin-4-one (**3h**)*: Yellow solid; 197 mg; Yield 63%; mp: 165-173℃; IR (ν cm^{-1}) = 3026 (w), 2915 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 780 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 3H), 7.45 (m, 6H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.85 (s, 1H), 4.41 (d, *J* = 16.2 Hz, 1H), 4.05 (d, *J* = 16.2 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.6, 157.1, 156.1, 150.5, 148.9, 139.6, 138.2, 137.7, 131.3, 130.3, 129.9, 129.9, 129.6, 129.1, 128.5, 127.2, 126.8, 126.0, 123.2, 119.7, 118.6, 56.0, 33.8, 21.4, 21.2; GCMS for $C_{29}H_{24}N_4OS_2$ (*m/z*) = 508.1.

*2-(1,3-Diphenyl-N-pyrazol-4-yl)-3-(4-methoxylphenylthiazol-2-yl)thiazolidin-4-one (**3i**)*:Yellow solid; 185 mg; Yield 71%; decomposed >187 ℃; IR (ν cm^{-1}) = 3025 (w), 2978 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 778 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.87 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.56 - 7.51 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 4H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.42 (d, *J* = 16.2 Hz, 1H), 4.06 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 172.8, 172.6, 171.0, 170.6, 159.5, 156.1, 150.4, 148.8, 139.4, 132.9, 129.9, 129.5, 128.9, 128.6, 127.4, 127.0, 126.9, 123.5, 118.7, 114.3, 107.4, 55.6, 54.4, 33.8; GCMS for $C_{28}H_{22}N_4O_2S_2$ (*m/z*) = 510.1.

*2-(3-(4-Chlorophenyl)-N-phenyl--pyrazol-4-yl)-3-(4-methoxylphenylthiazol-2-yl)thiazolidin-4-one (**3j**)*: Yellow solid; 181 mg; Yield 69%; mp: 120-128℃; IR (ν cm^{-1}) = 3025 (w), 2925 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 778 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.54 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.30 (t, *J* = 9.9 Hz, 1H), 6.90 (s, 1H), 6.81 (d, *J* = 11.0 Hz, 2H), 4.49 (d, *J* = 16.2 Hz, 1H), 4.07 (d, *J* = 16.3 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.5, 159.5, 156.9, 156.1, 149.2, 148.7, 139.4, 133.7, 131.8, 130.3, 130.0, 129.5, 127.8, 127.4, 127.4, 127.1, 126.8, 123.6, 118.7, 114.2, 107.5, 55.7, 55.6, 33.8; GCMS for $C_{28}H_{21}ClN_4O_2S_2$ (*m/z*) = 544.0.

*2-(1,3-Diphenyl-N-pyrazol-4-yl)-3-(4-bromophenylthiazol-2-yl)thiazolidin-4-one (**3k**)*: Yellow solid; 194 mg; Yield 74%; mp: 180-189 ℃; IR (ν cm^{-1}) = 3025 (w), 2925 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 778 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.89 (s, 1H), 7.88 (dd, J_1 = 7.8 Hz, J_2 =1.9 Hz, 2H), 7.79 (s, 1H), 7.76 -7.72 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 2H), 7.57 - 7.53 (m, 1H), 7.49 - 7.43 (m, 6H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 4.44 (d, *J* = 16.1 Hz, 1H), 4.05 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.7, 157.1, 156.5, 150.4, 147.7, 139.6, 133.2, 132.9, 131.9, 131.8, 129.9, 129.4, 128.9, 129.0, 128.6, 128.0, 127.4, 127.0, 123.3, 121.5, 118.6, 110.4, 55.9, 33.8; GCMS for $C_{27}H_{19}BrN_4OS_2$ (*m/z*) = 558.0.

2-(3-(4-Fluorophenyl)-N-phenyl--pyrazol-4-yl)-3-(4-bromophenylthiazol-2-yl)thiazolidin-4-one (***3l***): Yellow solid; 220 mg; Yield 74%; mp: 179-187℃; IR (ν cm^{-1}) = 3045 (w), 2930 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 812 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.89 (s, 1H), 7.88 (d, *J* = 9.6 Hz, 2H), 7.80 - 7.75 (m, 3H), 7.51 - 7.44 (m, 9H), 7.30 (t, *J* = 7.4 Hz, 1H), 4.45 (d, *J* = 15.7 Hz, 1H), 4.07 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.8, 163.7, 161.6, 157.1, 156.6, 149.3, 147.7, 139.5, 133.3, 131.9, 130.7, 129.9, 129.3, 128.0, 127.6, 127.1, 123.2, 121.5, 118.7, 118.7, 116.5, 116.3, 110.5, 55.8, 33.8; GCMS for $C_{27}H_{18}ClFN_4OS_2$ (*m/z*) = 576.0.

2-(3-(4-Bromophenyl)-N-phenyl--pyrazol-4-yl)-3-(4-chlorophenylthiazol-2-yl)thiazolidin-4-one (***3m***): Yellow solid; 190 mg; Yield 79%; mp: 182-190℃; IR (ν cm^{-1}) = 3025 (w), 2925 (w), 1690 (s), 1598 (w), 1504 (s), 1219 (s), 823 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.88 (s, 1H), 7.88 (d, *J* = 9.6 Hz, 2H), 7.70 - 7.71 (m, 3H), 7.50 - 7.44 (m, 9H), 7.32 (t, *J* = 7.4 Hz, 1H), 4.44 (d, *J* = 15.7 Hz, 1H), 4.10 (d, *J* = 16.3 Hz, 1H): ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.9, 163.7, 161.5, 157.1, 156.6, 149.3, 147.6, 139.5, 133.1, 131.9, 130.7, 129.9, 129.2, 127.9, 127.6, 127.1, 123.2, 121.5, 118.7, 118.4, 116.5, 116.2, 110.5, 55.8, 33.8; GCMS for $C_{27}H_{18}BrClN_4OS_2$ (*m/z*) = 591.9.

2-(3-(4-Methylphenyl)-N-phenyl--pyrazol-4-yl)-3-(4-bromophenylthiazol-2-yl)thiazolidin-4-one (***3n***): Yellow solid; 179 mg; Yield 74%; decomposed >210℃; IR (ν cm^{-1}) = 3025 (w), 2925 (w), 1687 (s), 1598 (w), 1504 (s), 1234 (s), 775 (s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.89 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.79 (s, 1H), 7.76 - 7.72 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 2H), 7.49 - 7.43 (m, 6H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 4.41 (d, *J* = 16.2 Hz, 1H), 4.05 (d, *J* = 16.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 170.8, 163.1, 161.1, 150.5, 148.9, 139.6, 138.2, 137.7, 131.3, 130.3, 129.9, 129.6, 129.1, 128.5, 127.2, 126.8, 126.0, 123.2, 119.7, 118.6, 56.0, 33.8, 21.4, 21.2; GCMS for $C_{28}H_{21}BrN_4OS_2$ (*m/z*) = 572.0.

2.3. Method for Determination of COX-1/COX-2

Screening assay directly measures PGP2α by stannous chloride reduction of COX-derived PGH2 produced in the COX reaction.[29] The reaction system consists of reaction buffer, haem, enzyme and synthetic compounds pre-incubated at 37°C for twenty minutes with background and enzyme controls. The reaction was initiated with the addition of arachidonic acid and incubated for two minutes at 37°C. The reaction was stopped with addition of saturated stannous chloride solution and five minutes at room temperature.The prosatgalndins are quantified by EIA. An aliquot of these reactions were added to the precoated plates in five-fold together with AChE tracer and antiserum and incubated for 18 hrs at room temperature on an orbit shaker. The plate was them finally developed with Ellman`s Reagent and kept on an orbit shaker in the dark room temperature for 60 min. The absorbance was read at 420 nm. The data was plotted as % B/B_0 (Standard Bound / Maximum Bound) versus log of concentration using a 5-parameter curve with appropriate dilutions and used to calculated the percent inhibition as per the formula given below,

Percentage Inhibition (%) = (Activity of Control – Activity of Test) / Activity of Control x 100

2.4. Molecular Docking Study

Docking simulations were performed to reveal the binding modes of synthesised compounds 3a-n with COX-2 enzyme. The structure of the human COX-2 enzyme[30] was directly downloaded from the protein data bank (PDB ID: 6BI4). Initially, the heteroatoms and water molecules of protein were removed, and polar hydrogens were added using Biovia Discover Studio.[31] The 2D structure of synthesized compounds were drawn and individual structure was analyzed by using ChemDraw Professional 15.0. During the optimization procedure all the parameters were set in order to obtain a stable structure with minimum energy. The docking simulation was conducted using Autodock 4.2.6 software.[32] The docking center was set to be the center of protein and the docking pocket size was set to be large enough to cover the whole protein molecule. The docking simulations were performed by configuring 3D grid box with center_x = -56.940568; center_y = -104.770909, center_z =

56.376182, size_x = 20, size_y = 20 and size_z = 20. The docking results were visualized using Discovery studio (Dassault Syst_emes, San Diego).[31]

3. Results and Discussion

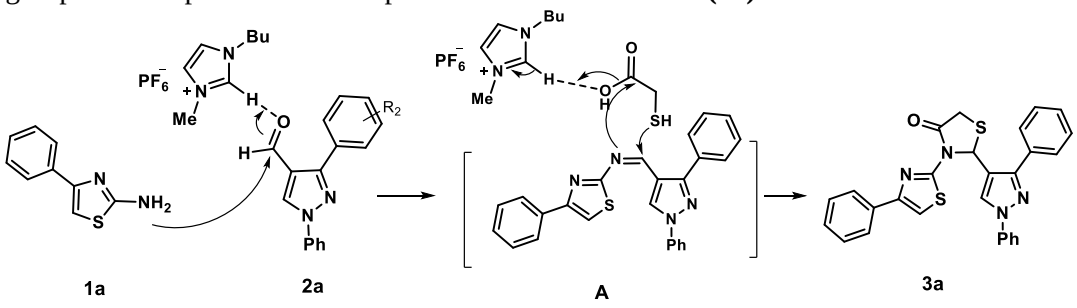
In continuous of our previous work to synthesis the bioactive heterocyclic compounds,[33-36] we started our experiment with 2-amino-thiazole **(1)**, pyrazole-3-aldehyde **(2)** and mercaptoacetic acid. It was observed that the multi-component reaction involving substrates **1a**, **2a**, and mercaptoacetic acid proceed effectively in ionic liquid, specifically 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6], resulting in the formation of the corresponding 2-pyrazole-*N*-thiazole-thiazolidin-4-one. The yield of requisite product **3a** increased with the increase of the temperature at 120 °C. Mainly, two ionic liquids *viz* [bmim][PF_6] and [bmim][BF_4], were studied for one-pot synthesis of thiazolidin-4-ones. Notably, [bmim][PF_6] afforded good result presumably due to its hydrophobic activation activity. It was assumed that water generated *in situ* in the condensation process exhibits miscibility with the hydrophilic ionic liquid [bmim][BF_4], thereby inhibiting the reaction from proceeding to completion. In contrast, the hydrophobic characteristics of [bmim][PF_6] would establish a micro-environment that facilitates the equilibrium by expelling water from the ionic liquid phase, thereby culminating in an enhanced conversion rate. In the course of our investigation to study the effect of the solvent for one-pot reaction, we found that the reaction did not proceed with acetonitrile, dimethylformamide, dichloromethane, and diphenyl ether. Compared with dichloromethane, ethanol, and tetrahydrofuran in ionic liquids demonstrated a remarkable increase in the reactivity with reduce in reaction time and a significant increase in outcome yield. To our delight, without use of solvent gave the similar results. Therefore, it is not a solvent of choice for sustainable chemistry. However, [bmim][PF_6] is non-volatile and easy to handle, therein acting as a benign and efficient medium. To investigate the reusability of the ionic liquid, **3a** was obtained by thorough extraction with ethyl acetate and the remaining ionic liquid phase was recycled in subsequent reactions. The recovered ionic liquid was employed for five cycles without any discernible loss of its functional efficacy (Table 1).

Table 1. Recycling of ionic liquid for one-pot three component synthesis of 2-pyrazole-*N*-thiazole-thiazolidinone at 120°C

Run	1	2	3	4	5
Yield[a]	87[b]	87	84	82	80

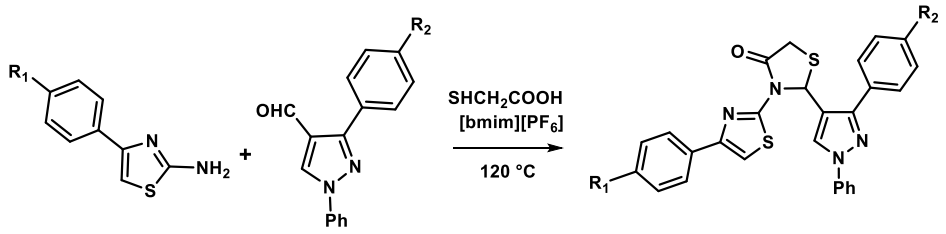
[a]All reactions were carried out with 25 mmol of substrate **1a**
[b]Isolated yield

The plausible mechanism is represented in Scheme 1. The ionic liquid can activated the carbonyl moiety of the pyrazole-2-aldehyde and mercaptoacetic acid whereas NH_2 moiety depolarized. Then the activated amino group of 2-amino-thiazole **1a** can carry out nucleophilic attack on carbonyl functionality of pyrazole-2-aldehyde **2a**, followed by the elimination of water, thus forming the imine intermediate (**A**). Then, sulphur of mercaptoacetic acid attacks the carbon atom of the imine intermediate (**A**) and the nitrogen atom of imine functionality performs an intramolecular attack on the COOH group of mercaptoacetic acid to produce thiazolinin-4-ones **(3a)**.[37]



Scheme 1. Plausible reaction mechanism

Encouraged by the results obtained above, we extended this process to various aldehyde and amine substrates to gain more insight into this reaction (Scheme 2). It turned out that in [bmim][PF_6], various aldehyde and amine substrates reacted smoothly with mercaptoacetic acid and afforded the corresponding 2,3-disubstituted-1,3- thiazolidi-4-ones (**3a-n**) in good to excellent yields.



1 2 3

Entry	R_1	R_2	Time (h)	Yield[b] (%)
3a	H	H	5	76
3b	H	F	5	80
3c	H	Cl	5	88
3d	H	Me	5	79
3e	Me	H	8	56
3f	Me	F	8	61
3g	Me	Cl	8	63
3h	Me	Me	8	71
3i	OMe	H	8	69
3j	OMe	Cl	8	74
3k	Br	H	4	74
3l	Br	F	4	76
3m	Br	Cl	4	79
3n	Br	Me	4	74

[a]All reactions were carried out with 25 mmol
[b] Isolated yield

Scheme 2. One-pot three component synthesis of 2-pyrazole-*N*-thiazole-thiazolidinone[a]

All compounds were evaluated for inhibition assay for COX-1 and COX-2 enzymes using the COX-1 (human) Inhibitor Screening Assay Kit and COX-2 (human) Inhibitor Screening Assay Kit (Cayman Chemical Company, Ann Arbor, MI, USA).[29] At the used concentrations, all synthesized compounds showed potent inhibitory activities at both COX enzymes, as shown in table 2. At 5 μM concentration, all compounds shows an inhibitory percentage higher than 54.6% against the COX-2 enzyme, while the inhibitory percentage against the COX-1 enzyme for all compounds was in the range of 59.5 - 31.2%. However, the most potent compound against the COX-1 and COX-2 enzyme was **3j** and **3i**, with an inhibitory percentage of 48.9% and 89.5% respectively in comparison with the positive control celecoxib. The **3b**, **3d**, **3h**, and **3k** were found to be most selective compounds. The inhibitory percentage of **3b** against COX-2 was 79.6% and inhibitory percentages COX-1 was 43.2% respectively at 5 μM concentration. The selectivity index of compound **3b** may be due to the presence fluoro-funcionality at benzyl ring of pyrazole moiety. When fluoro-funcionality is replaced by methyl, selectivity index of compound **3d** showed 1.88. The presence of electron donating group such as methyl at *p*-position of phenyl ring of pyrazole and thiazole moiety (compound **3h**) showed selectivity index 1.88. However, the bromo-functionality at phenyl ring of thiazole moiety showed selectivity index of compound **3k** was 1.88. All of the tested compounds showed selectivity toward the COX-2 enzyme. Moreover, the selectivity index were calculated and shown in table 2, the selectivity index of compounds **3a-n** were found in the range of 1.51 to 2.61 respectively in comparison with the positive control celecoxib having selective index:1.88.

Table 2. Selective index and inhibition concentration values

Entry	COX-1 ± SEM	COX-2 ± SEM	Selective Index COX-2/COX-1
3a	31.73±2.11	81.33±1.87	2.56
3b	43.29±2.20	79.63±2.09	1.83
3c	59.51±3.21	83.04 ±3.21	1.39
3d	36.21±2.17	68.29±2.02	1.88
3e	44.02±2.23	73.53±2.62	1.67
3f	37.80±2.60	75.24±2.68	1.99
3g	51.82±2.88	78.29±2.89	1.51
3h	42.31±2.77	79.63±2.81	1.88
3i	34.02±2.15	89.51±2.13	2.61
3j	48.90±2.86	75.73±2.71	1.54
3k	43.29±2.31	81.46±3.12	1.88
3l	35.12±2.19	63.53±2.62	1.80
3m	48.41±2.88	77.43±2.61	1.59
3n	31.32±1.89	54.63±1.82	2.56
Celecoxib	48.31±2.77	91.09±1.77	1.88

Molecular docking simulations were performed with the entire synthesised thiazoline-4-one compounds; to predict the binding interaction of these compounds in the active site of COX-2 enzyme (Table 3). It was observed that substituted thiazoline-4-one **3a, 3d, 3e, 3h, 3i, and 3k** recognized the binding pocket of enzyme correctly. These compounds formed stable key interactions with the active sites of enzymes. The docking score process mainly utilized simple scoring functions which aim to gather the leading interactions. In the case of docking of molecular with COX-2, the binding affinities of substituted thiazoline-4-one were in the order **3d = 3e** (-9.3 kcal/mol) > **3k** (-9.2 kcal/mol) > **3a** (-9.1 kcal/mol) > **3h** (-8.3 kcal/mol). The compound **3d** with the most promising *in-vitro* activity (selective index: 1.88) also demonstrated better binding free energy value. Similar observation was made in the case of compound **3a** and **3h**.

The protein-ligand complex analysis of compound **3a** shown in Figure 1 and there were mainly hydrophobic interactions occur between phenyl ring with Leu93 and Val116 *via* π-σ interactions and π-π T-shaped interactions were found between benzyl ring with Tyr115. Also, π-alkyl interactions were observed in thiazoline-4-one ring of **3a** with Val89, Ile112, and Pro84. Including, significant π-sulphur interaction was observed with Trp100. The highest bond length was observed from thiazolidinone and benzyl ring (5.26 A°) while shortest bond length was observed from phenyl and Val116 (3.32 A°). Similar type of hydrophobic interactions were found in compound **3b** and **3c** while highest bond length was observed from thiazolidinone and Trp100 through π-sulphur in **3b** (5.99 A°). The individual π-σ interactions were found in between *N*-phenyl ring of pyrazole with Leu93 and Val116 in compound **3d** (Figure 1). Including, π-π T-shaped interaction was observed phenyl ring of thiazolidinone and Tyr115, whereas the inter-hydrophobic interactions were also found in compound **3d**. The four π-alkyl interactions were observed with Leu93, Ile112, Val89, and Pro84. The highest bond length was observed within the aryl groups of the **3d** (5.58 A°) while shortest bond length was observed from phenyl and Val116 (3.31 A°). Similar type of interactions was observed in compound **3e** except π-alkyl hydrophobic interaction was generated with Ile112 and thiazolidinone framework (Figure 1). The protein-ligand complex analysis of compound **3f, 3g** and **3h** showed electrostatic interaction between *N*-phenyl ring of the pyrazole and Arg120 (bond length: 3.70 A°). This is may be due to presence of methyl-functionality present in the phenyl ring. The hydrophobic interaction occur *via* four π-σ stacked interaction with Val89 and Leu93; two π-π interaction within compound and four π-alkyl interactions were observed with Val89, Leu93, and Val116 in between the requisite compounds. The presence of methoxy group in the thiazolidinone frame of compound **3i** and **3j** were able to produced conventional hydrogen bond with Glu524 and Tyr355 respectively (bond length: 3.57 A° and 3.27 A° for compound **3i** and **3j** respectively). However, the effect of bromo-functionality did

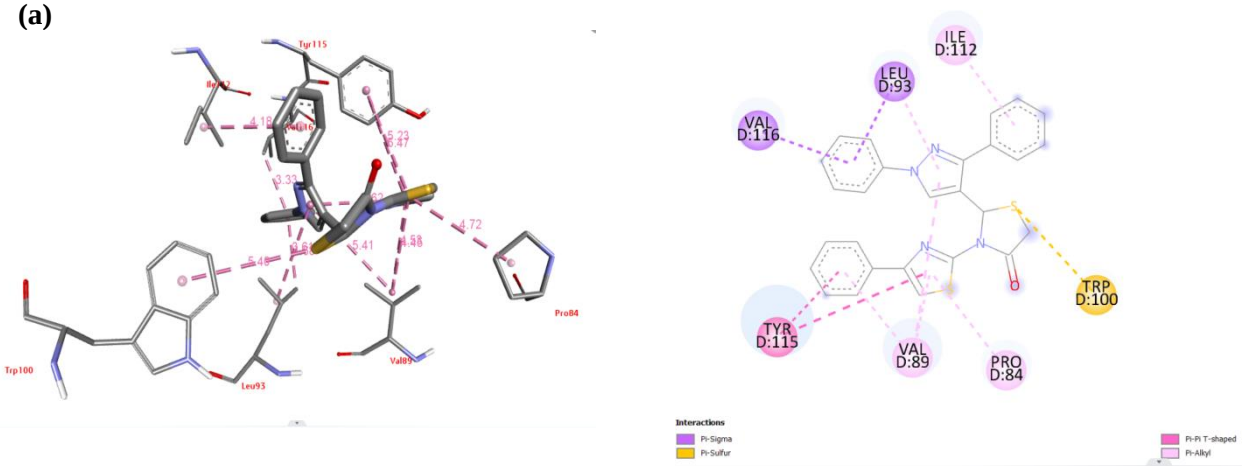
not affect the types of interactions in comparison with other compounds. The similar types of interactions were observed with compounds **3k, 3l, 3m** and **3n.**

Table 3. Molecular docking results of synthesized compounds against COX-2 (PDB ID 6BI4)

Entry	Binding affinity Kcal/mol	Interacting amino acids			
		Hydrogen bond	Electrostatic	Hydrophobic	Other
3a	-9.1			Leu93, Val116, Tyr115, Val89, Ile112, Pro84	Trp100
3b	-7.8			Val89, Leu93, Ile112,Val116: Tyr115, Pro84	Trp100
3c	-7.2			Val89, Leu93, Val116, Tyr115, Tyr355, Val89, Pro84	Trp100
3d	-9.3			Leu93, Val116, Tyr115, Ile112, Val89, Pro84	Trp100
3e	-9.3			Leu93, Val116, Tyr115, Val89, Leu93, Ile112, Pro84	Trp100
3f	-8.4		Arg120	Val89, Leu93, Tyr115, Val116	Tyr115
3g	-8.1		Arg120	Val89, Leu93, Ala527, Tyr115, Val116	Tyr115
3h	-8.3		Arg120	Val89, Leu93, Ala527, Tyr115, Val116	Tyr115
3i	-9.3	Glu524		Leu93, Val116, Tyr115, Val89, Pro84, Ile112	Trp100
3j	-7.8	Tyr355	Arg120	Val89, Leu93, Tyr115, Val523, Val89, Val116,	Tyr115
3k	-9.2			Val89, Leu93, Val116, Tyr115, Pro84, Ile112	Trp100
3l	-8.4		Arg120	Val89, Leu93, Tyr115, Tyr115, Val89, Val89, Leu93,Val116	Tyr115
3m	-6.3			Val89, Leu93, Ile92, Pro84, Val116, Ile112	Trp100
3n	-8.3		Arg120	Val89, Leu93, Tyr115, Ala527, Leu93, Val116,	Tyr115

Novel thiazolidinones containing pyrazole and thiazole hybrid compounds

(a)



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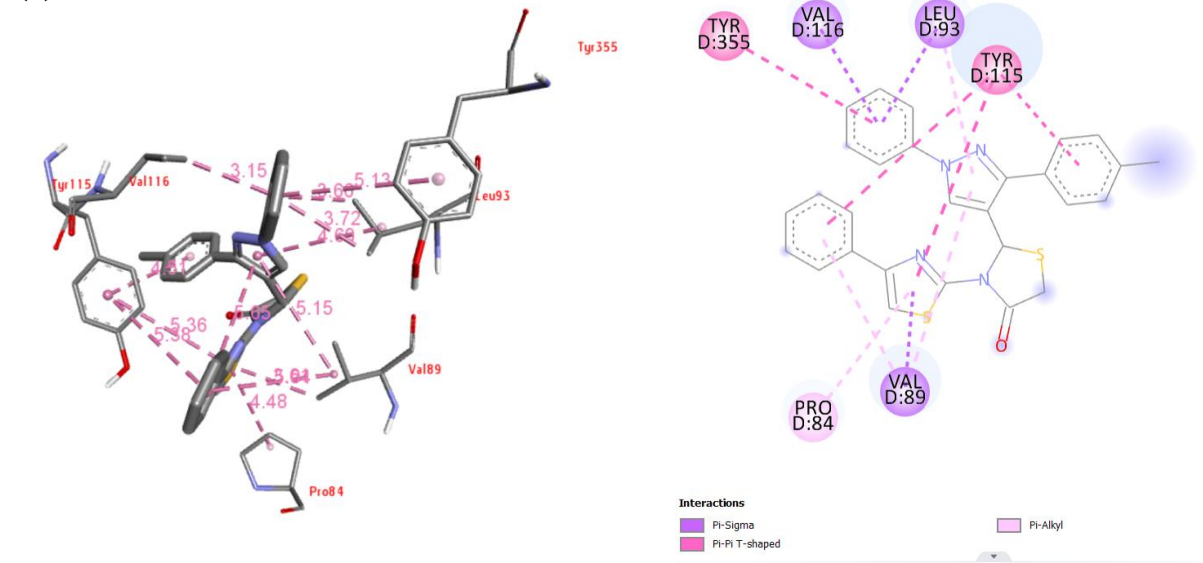

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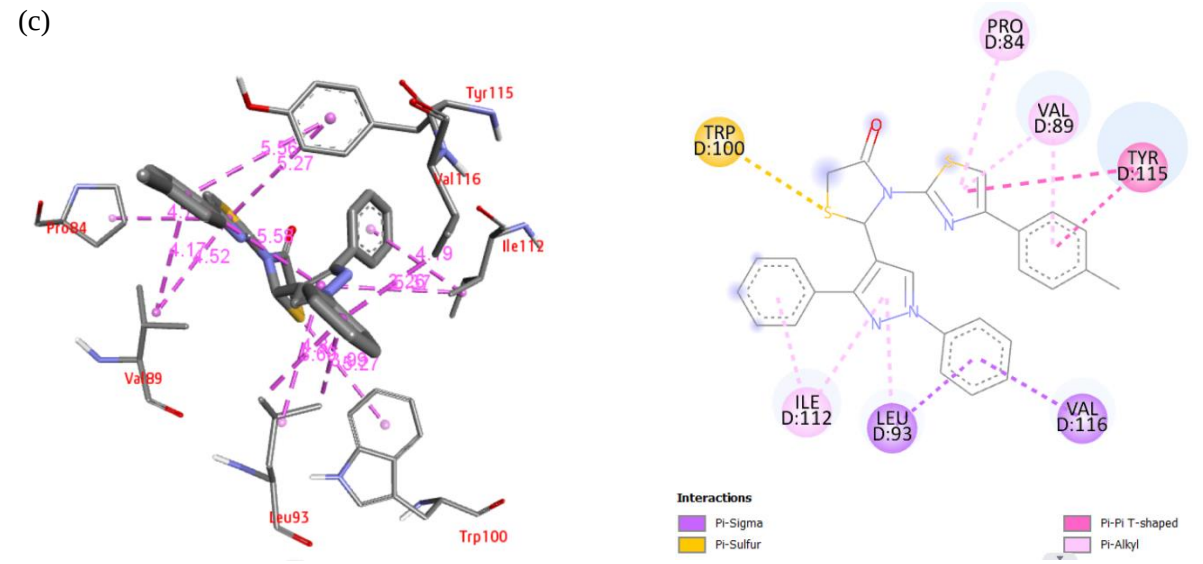

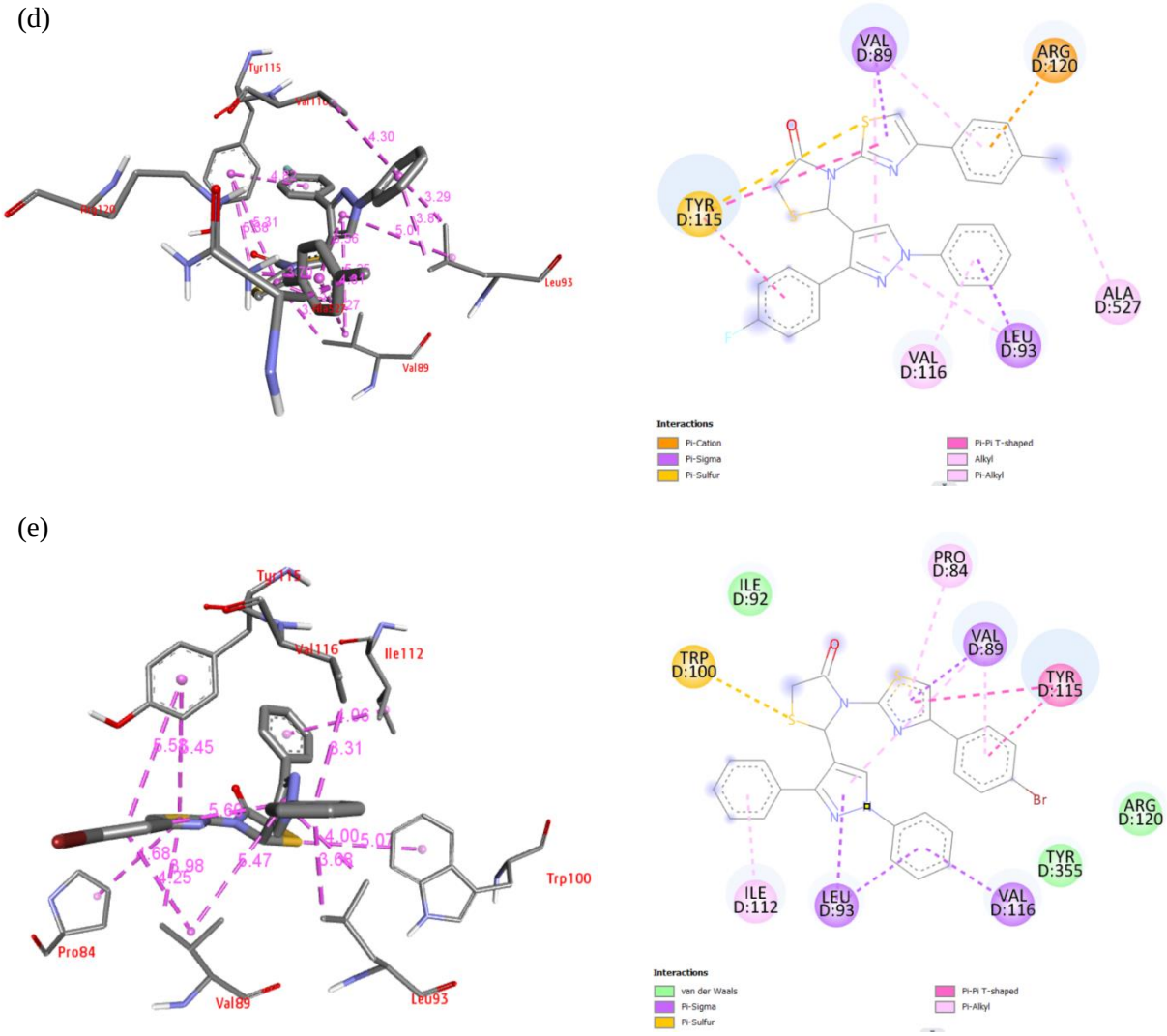

Figure 1. Binding interaction of (a) **3a**, (b) **3d**, (c) **3e**, (d) **3h,** and (d) **3k** with COX-2 (PDB ID 6BI4)

5. Conclusion

In summary, the present study reports successful design and synthesis of a new class of 2-pyrazole-*N*-thiazole-thiazolidinone hybrid skeleton. A diverse range of structural variations of aromatic moiety was demonstrated in the scope of the synthesized derivatives. All the synthesized derivatives exhibited good to moderate inhibitory activity. Meanwhile, derivatives 3h and 3k demonstrated exceptional selectivity in both instances when assessed against the standard pharmacological agent, celecoxib. The molecular docking analyses elucidated the conceivable binding energies of the synthesized compounds within the pocket site of the enzymes. This study also identified a new class of 2-pyrazole-*N*-thiazole-thiazolidinone derivatives as cyclooxygenase inhibitors.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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