Journal Pre-proofs

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Synthesis of Novel of 2, 5-disubstituted 1, 3, 4- Oxadiazole derivatives and their *In Vitro* anti-inflammatory, anti-oxidant evaluation, and Molecular Docking Study

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ABSTRACT

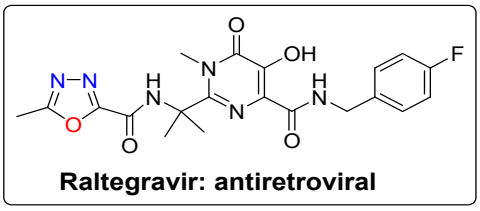
A series of novel 2, 5-disubstituted 1, 3, 4- Oxadiazole derivatives as a potential anti-inflammatory, and anti-oxidant agent were synthesized *via* cyclisation. Hydrazide molecule treated with substituted acids in the presence of phosphorus oxychloride ($POCl_3$) as an efficient reagent as well as solvent by conventional method with shorter reaction time and excellent yield. The newly synthesized 1, 3, 4-oxadiazole derivatives exhibited excellent to good anti-inflammatory and anti-oxidant activities compaired to the standard drugs. Molecular docking study on the crucial anti-inflammatory target–cyclooxygenase-2 (COX-2) revealed the ability of the scaffold to correctly recognize the active site and achieve significant bonded and non-bonded interactions with key residues therein. This study could identify potential compounds which can be pertinent starting points for structure-based drug design to obtain newer anti-inflammatory agents.

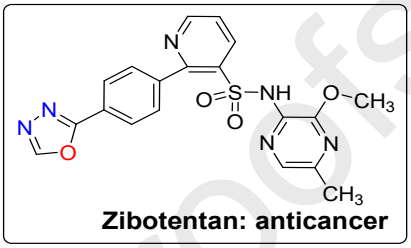
Keywords: 1, 3, 4- Oxadiazole, anti-inflammatory, anti-oxidant, Biological activity, Computational Chemistry.

Compounds containing heterocyclic ring systems are of great importance both medicinally and industrially. During the last few decades, biological activities, synthesis and transformations of five membered heterocyclic compounds have received considerable attention and importance due to their remarkable and wide variety of applications. Oxadiazole are frequently occurring motifs in drug like molecules. Due to their remarkable unique properties and have been frequently employed in drug synthesis such as including raltegravir, butalamine, fasiplon, oxolamine, and pleconaril.

Substituted oxadiazole and its derivatives constitute an important family of heterocyclic compounds with biological and pharmacological properties like antibacterial[1-6], fungicidal[7-9], antimicrobial[10-13], anti-inflammatory[14,15], anticonvulsant[16,17], anticancer[18,19], antimalerial[20], and antidepressant[21]. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids,

esters and carboxamides[22]. The therapeutic importance of these compounds prompted us to develop selective molecules in which the substituent could be arranged in a pharmacophore pattern to display higher pharmacological activities. In view of these observations and our continued interest in the synthesis of biologically active heterocyclic compounds[23]. Two examples of compounds containing the 1, 3, 4-oxadiazole unit currently used in clinical medicine are: Raltegravir an antiretroviral drug and Zibotentan an anticancer agent.



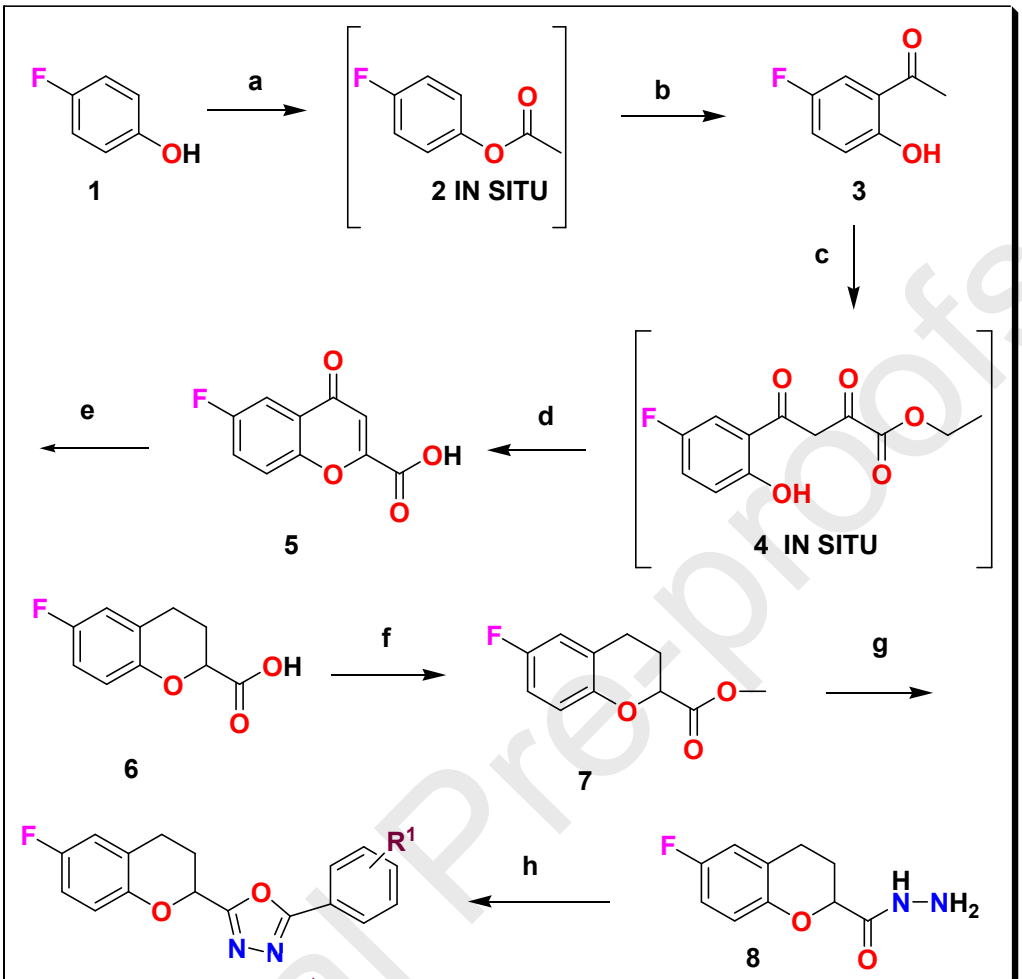


Structures of the API molecules with oxadiazole moieties

There are limited methodology exists for the synthesis of 1, 3, 4- oxadiazoles. A few one pot methods have been reported as the use of acetohydrazides or its derivative, as a source of two contiguous nitrogen atoms, and a variety of cyclizing agents[24]. Typically, the reaction is promoted by heat and anhydrous reagents including thionyl chloride[25], phosphorous pentoxide[26], triphenylphoshine[27], triflic anhydride[28], and phosphorous oxychloride[29]. Alternative synthetic methods comprise reaction of aceto hydrazides with keteneylidene triphenylphosphorane[30] or base promoted cyclization reaction of trichloroacetic acid hydrazones[31].

Compound **6** (Scheme I) obtained by esterification, rearrangement, acylation, cyclization, hydrolyzation[32-33], followed by hydrogenation[34] with an overall low yield. Reported conditions were not suitable for industrial application. Compound **3** synthesised by one pot Friedel Craft acetylation followed by Fries rearrangement from 4-fluoro phenol **1**. Base catalysed Claisen condensation of diethyl oxalate of **3** followed by acid catalyed cyclisation to afford **5** in situ. Compound **7** obtained by hydrogenation of compound **5** using Pd/C in acetic acid followed by esterification using H_2SO_4 in methanol**.** Compound **8** hydrazides obtained by hydrazinolysis of ester. Compound **8** was the key materials for the synthesis of 2, 5 disubstituted 1, 3, 4 oxadiazole by refluxing in $POCl_3$ with substituted aromatic carboxylic acid derivatives to afford final products **BK-12** to **BK-23** with overall moderate yield. Present process is mild, economic and industrially feasible using cheap raw materials. The effect of different dehydrating agents were disclosed in **Table 1** with respective to reaction time and yield studied for BK-12 (Scheme II). Structures of final BK-12 to BK-23 disclosed in **Table 2** with corresponding aromatic acids.

Scheme I: Schematic representation of route of synthesis of 2, 5-disubstituted 1, 3, 4 oxadiazole.



Scheme II: Synthesis of 2, 5-disubstituted 1, 3, 4 oxadiazole BK-12.

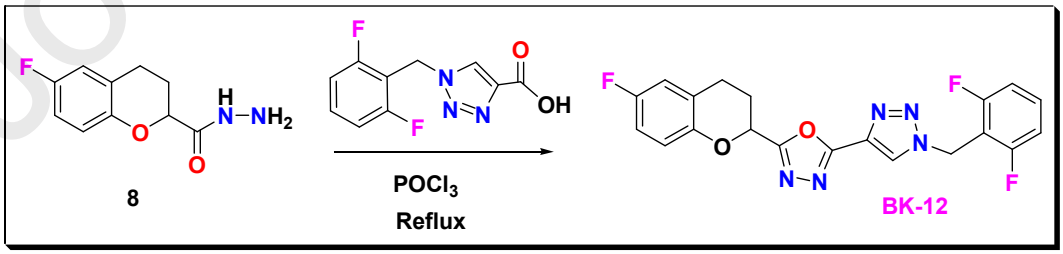
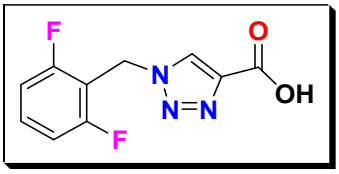
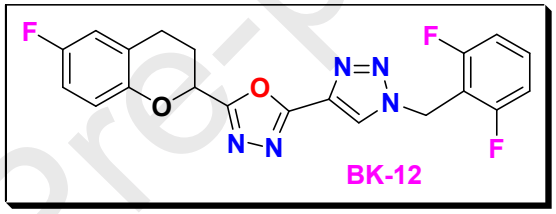
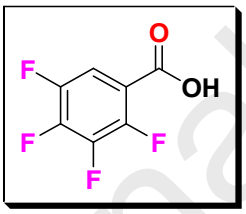
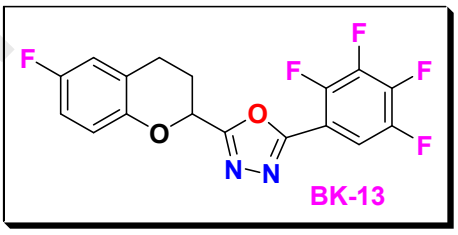
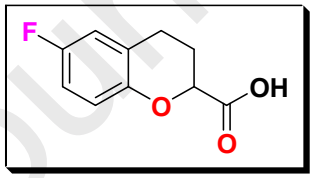
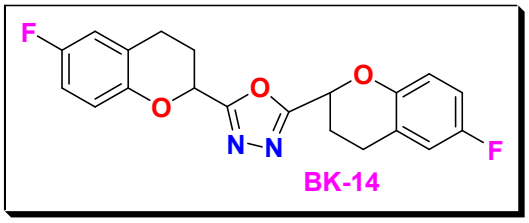
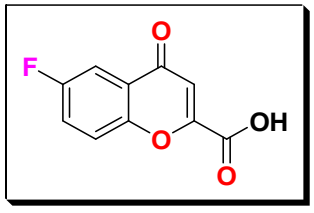
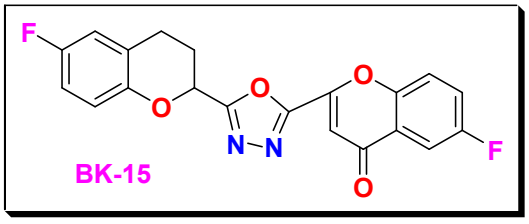
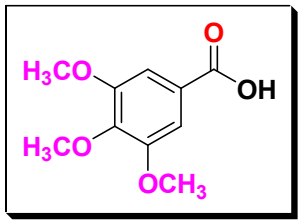
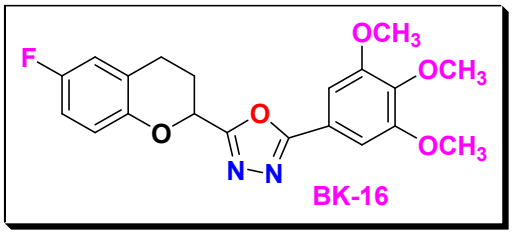
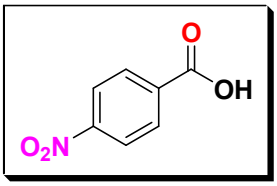
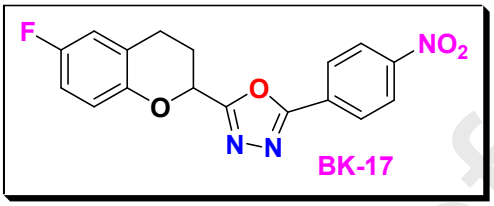
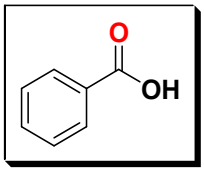
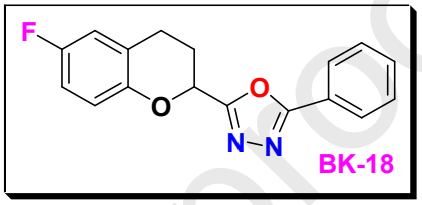
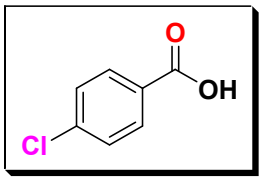
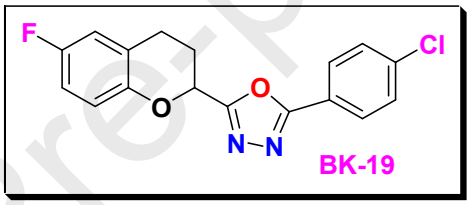
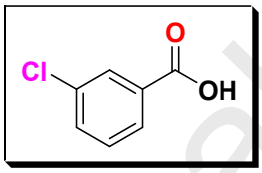
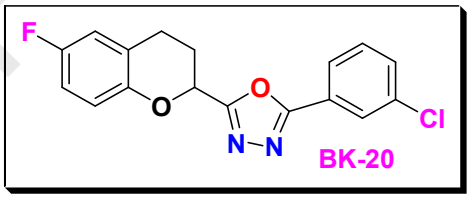
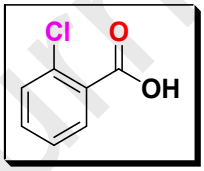
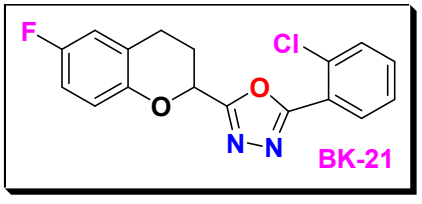
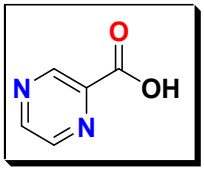
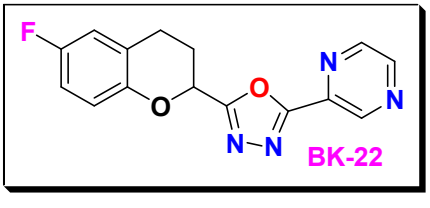


Table 1: Screening of different dehydrating agents and their effect on reaction time and yield for synthesis of BK-12 (Scheme II).

Cyclizing / Dehydrating Agents	Reaction time in hrs	% Yield for BK-12
Thionyl chloride	13 hrs	41
Phosphorus pentoxide	18 hrs	33
Triphenylphoshine	20 hrs	---
Triflic anhydride	15 hrs	45
Polyphosphoric acid	18 hrs	48
Phosphorus oxychloride	6 hrs	85

Table-2 Synthesized compounds of 2, 5-disubstituted 1, 3, 4-oxadiazole

Aromatic Acid R'	Product
	 BK-12
	 BK-13
	 BK-14
	 BK-15

	 BK-16
	 BK-17
	 BK-18
	 BK-19
	 BK-20
	 BK-21
	 BK-22

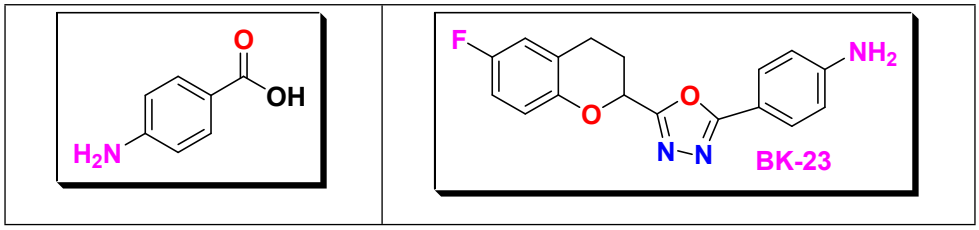


Table 3. In vitro Anti-oxidant and anti-inflammatory activities result of compounds BK-12 to BK-23 in tabular form.

Test Samples	Anti-oxidant		Anti-inflammatory $IC_{50}/\mu M$
	DPPH $IC_{50}/\mu M$	Nitric oxide $IC_{50}/\mu M$	
Control	------	------	------
Ascorbic acid	44.18 ± 0.78	42.63 ±0.64	------
Diclofenac sodium	------	------	90.21 ± 0.77
BK-12	**23.07** ±0.27	88.04 ±0.71	86.23 ±0.91
BK-13	**28.99** ±0.68	85.86 ±0.21	99.82 ±0.94
BK-14	**28.99** ±0.79	86.95 ±0.34	74.31 ±0.74
BK-15	34.91 ±0.81	73.91 ±0.45	**56.70** ±0.31
BK-16	43.19 ±0.95	86.95 ±0.61	**62.21** ±0.59
BK-17	**28.69** ±0.63	84.78 ±0.24	78.72 ±0.85
BK-18	**28.69** ±0.70	85.86 ±0.77	72.30 ±0.94
BK-19	**17.15** ±0.12	85.86 ±0.85	90.65 ±0.88
BK-20	40.82 ±0.50	88.04 ±0.66	**58.54** ±0.26
BK-21	**23.07** ±0.61	84.78 ±0.68	69.55 ±0.70
BK-22	73.37 ±0.80	86.95 ±0.72	73.22 ±0.63
BK-23	34.91 ±089	89.13 ±0.70	**45.69** ±0.37

Compounds in bold blue shade showing excellent activities. All the compounds having error bars in the range of $IC_{50}/\mu M$ (± 0.10 to 0.95)

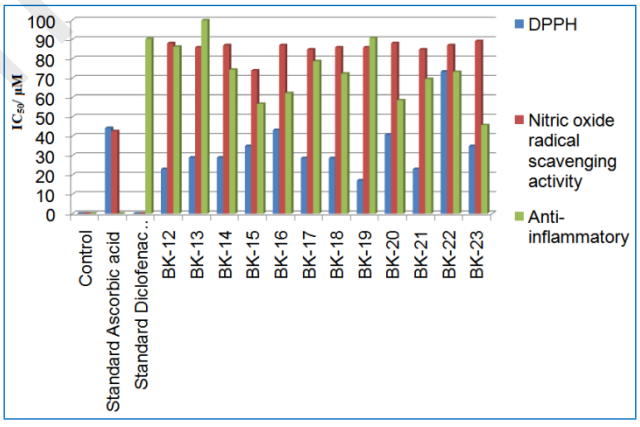


Chart-1: anti-oxidant and anti-inflammatory activities result of compounds BK-12 to BK-23.

Antioxidant screening results

The results of the antioxidant activity screening of the tested compound for DPPH (2, 2-diphenyl-1-picrylhydrazyl) and Nitric oxide radical scavenging activities were also summarized in **Table 3** and **Chart 1**. All the newly synthesized compounds **BK-12 to BK-23** shows good to moderate antioxidant activity as compared to the standard drug Ascorbic acid (**Table 3**). According to the DPPH assay analysed in triplicate, compounds with IC_{50} values of **BK-19** (17.5), **BK-12** (23.07), **BK-21** (23.07), **BK-17** (28.69), **BK-18** (28.69)**, BK-13** (28.99) and **BK-14** (28.99) μM/mL respectively, exhibited promising radical scavenging activities when compared with synthetic antioxidant ascorbic acid (IC_{50} = 44.18μM/mL). From the synthesized compounds with IC_{50} values (17.5 to 28.99μM/mL) showed the best DPPH radical scavenging activity, while compound BK-22 showed the lowest activity when compared with ascorbic acid. From the IC_{50} data it is clear that presence of 4-chloro benzene at 5 position of oxadiazole exhibit better activity as compaired to 2- chloro (BK-20) and 3-chloro (BK-21) substituent and also hybrid molecule like BK-12 are excellent potent as compaired to others for DPPH radical scavenging activity.

All the compounds BK-12 to BK-23 are showing very poor antioxidant activity for Nitric oxide radical scavenging activity compared to reference standard drug ascorbic acid.

Anti inflammatory screening results

The results of the anti-inflammatory activity screening of the tested compound were also summarized in **Table 3** and **Chart 1**. 2, 5 di-substituted 1,3,4-oxadiaxole derivatives **BK-12 to BK-23** shows good to moderate anti-inflammatory as compared to the standard drug diclofenac sodium. According to the anti-inflammatory activities data analysed in triplicate, compounds with IC_{50} values of **BK-23** (45.69), **BK-15** (50.54), and **BK-20** (56.70) μM/mL respectively, are exhibited promising anti-inflammatory activities when compared with synthetic antioxidant diclofenac sodium (IC_{50} = 90.21μM/mL). From the synthesized compounds BK-23, BK-15 and BK-20 showed the best anti-inflammatory activity, while all the other compounds are showing comparable results to the standard drug diclofenac sodium.

Molecular Docking

Promising level of anti-inflammatroy activity demonstrated by the 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives discussed herein motivated us to elucidate the plausible mechanism by which they can exert the anti-inflammatroy activity. Furthermore to rationalize the obtained biological potency and establish an SAR based on these molecular docking study against the well known targets in the anti-inflammatory therapy i.e cyclooxygenase-2 (COX-2). COX-2

is an oxido-reductase having a role in prostaglandin biosynthesis and is a key mediator of inflammatory pathways owing to which it has gained special focus on anti-inflammatory research since past few decades. An isoform of COX family, COX-2 is highly inducible in response to proinflammatory stimuli, cytokines and consequential in exaggerated prostaglandin release. In the absence of available resources to carry out target-based assays, molecular docking has gained significant importance to identify the targets for ligands and the associated thermodynamic interactions that govern the moduclation of the target.

Molecular docking study showed that all the 2, 5-disubstituted 1, 3, 4- oxadiazole derivatives could snuggly fit in the active site cavity of COX-2 occupying energetically favourable position at the co-ordinates close to the co-crystallized ligand. They produced good to moderate binding affinities with docking scores ranging from -9.692 (glide binding energy of -45.531 Kcal/mol) for the active compound **BK-13** to -7.007 (glide energy -22.757 Kcal/mol) for a moderately active **BK-23** with an average docking score of -8.063 (glide energy -33.293 Kcal/mol) (**Table 4 in SI**). These binding affinity scores co-related well with the experimentally observed anti-inflammatory activity. Furthermore to gain a deeper insight into binding modes and nature of thermodynamic interactions influencing the anchoring of these molecules into the target, a per-residue interaction analysis was carried out which is elaborated in next section for the most active compound **BK-13** and is summarized for others in (**Table 4 in SI**).

The lowest energy docked conformation of **BK-13** showed that the molecule is deeply embedded into the active site of COX-2 (**Figure 1**) producing docking score of -9.692 (Glide energy -45.531 Kcal/mol) which is attributed to a set of close bonded (H-bonding) and non-bonded (steric and electrostatic) interactions with residues lining the active site. Quantification of per-residue interactions showed that the molecule is engaged in an extensive network of significant van der Waals interactions with Glu524 (-2.983 Kcal/mol), Val523 (-2.985 Kcal/mol), Arg513 (-2.884 Kcal/mol), Leu359 (-2.879 Kcal/mol), Tyr355 (-2.913 Kcal/mol), Ser353 (-2.979 Kcal/mol), Tyr348 (-2.991 Kcal/mol), Arg120 (-2.957 Kcal/mol), Leu117 (-2.996 Kcal/mol), Val116 (-2.966 Kcal/mol), Val89 (-2.972 Kcal/mol) through the 5-(2,3,4,5-tetrafluorophenyl)-1, 3, 4-oxadiazole component while the 6-fluoro-3,4-dihydro-2H-chromene component showed a similar type of interactions with Leu534 (-2.999 Kcal/mol), Leu531 (-2.988 Kcal/mol), Ser530 (-2.879 Kcal/mol), Ala527 (-4.379 Kcal/mol), Gly526 (-2.992 Kcal/mol), Met522 (-2.892 Kcal/mol), Phe518 (-2.980 Kcal/mol), Trp387 (-2.911 Kcal/mol), Tyr385 (-2.909 Kcal/mol), Phe381 (-3.906 Kcal/mol), Leu352 (-

2.969 Kcal/mol), Val349 (-2.995 Kcal/mol). The enhanced binding affinity of BK-13 is also attributed to signifcant coloumbic inerations with Glu524 (-2.956 Kcal/mol), Val523 (-2.944 Kcal/mol), Met522 (-2.963 Kcal/mol), Arg513 (-2.991 Kcal/mol), Tyr355 (-2.987 Kcal/mol), Ser353 (-2.936 Kcal/mol), Arg120 (-2.925 Kcal/mol) and His90 (-2.961 Kcal/mol) residues of the active site. Such a balanced network of steric and van der Waals interactions were observed for other molecules in the series as well (**Table 4 and Figure 1S-S11 in SI**). The compound **BK-13** was further stabilized into the active site of COX-2 through hydrogen bond between the oxygen of chromene ring and Ser530 (2.55Å) and a very close pi-pi stacking interactions with Tyr385 (2.618Å), which serve as "anchor" guiding the ligand into the active site of the target and compliment the steric and electrostatic interactions.

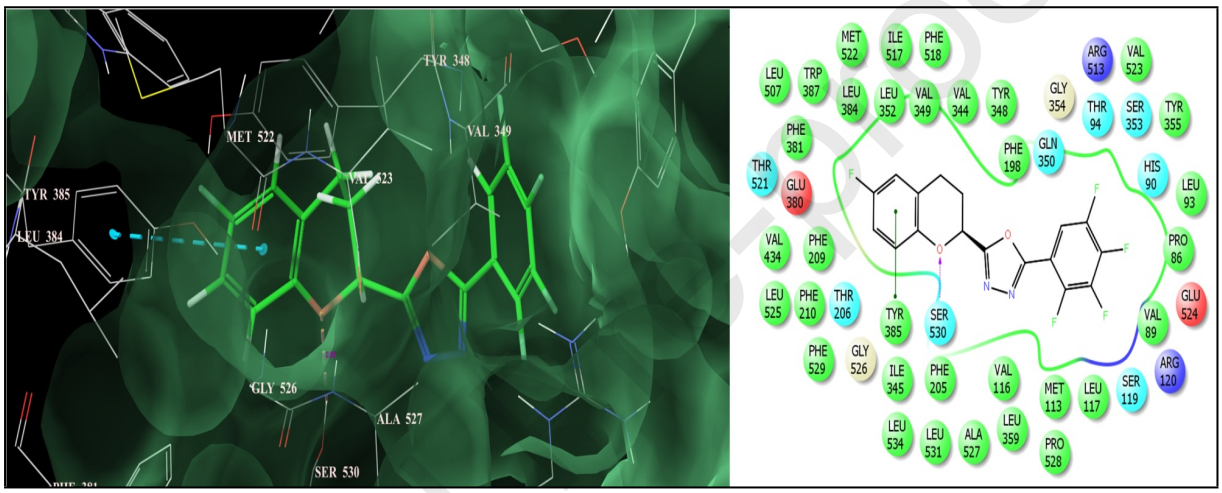


Figure 1: Binding mode of compound **BK-13** into the active site of cyclooxygenase 2 (COX-2) (on right side: green lines indicate π-π stacking interactions while the pink lines signify the hydrogen bonding interactions)

Overall the per-residue ligand interaction analysis suggests that steric complementarities along with electrostatic interactions with the residues lining active site of COX-2 contribute significantly to the mechanical interlocking of these molecules which could be fruitfully utilized to optimize these leads for obtaining tight binding candidates with high selectivity and specificity.

In silico ADME properties

The success of a drug is determined by good efficacy and acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft software[35]. A computational study of all the synthesized compounds was performed

for prediction of ADME properties and the value obtained is presented in Table 5. Absorption (% ABS) was calculated by: % ABS= 109-(0.345×TPSA)[36]. It is observed that compounds exhibited a good % ABS (% absorption) ranging from 76.58 to 92.39%. Furthermore, none of the synthesized compounds BK-12 to BK-23 violated Lipinski's rule of five (miLog *P* ≤ 5). A molecule likely to be developed as an orally active drug candidate should not show more than one violation of the following four criteria: miLog *P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5[37].

The larger the value of the drug likeness model score, the higher is also probability that the particular molecule will be active. All the tested compounds **BK-12 to BK-23** followed the criteria for orally active drug (**Table 5**) and therefore, these compounds may have a good potential for eventual development as oral agents.

Table 5. Pharmacokinetic parameters important for good oral bio-availability and drug likeness model score of the synthesized compounds **BK-12 to BK-23**.

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	
BK-12	81.79	78.88	4	328.75	413.36	3.27	7	0	0	0.78
BK-13	92.39	48.16	2	273.35	368.26	4.09	4	0	0	-0.05
BK-14	89.2	57.39	2	307.13	370.36	3.57	5	0	0	0.16
BK-15	81.97	78.37	2	303.10	382.32	2.82	6	0	0	1.12
BK-16	82.83	75.86	5	330.26	386.38	3.28	7	0	0	0.31
BK-17	76.58	93.98	3	276.95	341.30	3.61	7	0	0	0.16
BK-18	92.39	48.16	2	253.62	296.30	3.65	4	0	0	0.32
BK-19	92.39	48.16	2	267.16	330.75	4.33	4	0	0	0.36
BK-20	92.39	48.16	2	267.16	330.75	4.30	4	0	0	0.19
BK-21	92.39	48.16	2	267.16	330.75	4.28	4	0	0	0.53
BK-22	83.5	73.94	2	245.31	298.28	1.82	6	0	0	0.53
BK-23	83.41	74.18	2	264.91	311.32	2.73	5	2	0	0.32

% ABS: percentage absorption, TPSA: topological polar surface area, n-ROTB: number of

rotatable bonds, MV: molecular volume, MW: molecular weight, milogP: logarithm of partition coefficient of compound between n-octanol and water, n-ON acceptors: number of hydrogen bond acceptors, n-OHNH donors: number of hydrogen bonds donors.

The preliminary *In vitro* anti-oxidant, and anti-inflammatory screening results of novel 2, 5 di-substituted 1, 3, 4-oxadiaxole derivatives BK-12 to BK-23 reported here have emerged as highly potent anti-oxidant agents for DPPH, and very poor for Nitric oxide radical scavenging activity.The possible improvements in the activity can be further slight modifications in the substituents on the basic, 2, 5 di-substituted 1, 3, 4-oxadiaxole nucleus. The hybrid molecule like BK-12 having both moieties oxadiazole and triazole has very good activity and also compound BK-13 shows highly increased activity may be due to tetra fluro substitution on aromatic ring as compared to other substituent on aromatic ring which are present on novel 2, 5 di-substituted 1, 3, 4-oxadiaxole derivatives. All the other compounds showing very poor to comparable results for anti-oxidant, and anti-inflammatory activities as compared to the standard drug. Moreover, the molecular docking study showed that all the compounds bonded well with good binding energies to COX-2 enzyme qualifying the scaffold as a pertinent starting point for structure based drug design to for the development of new series of derivatives with potent anti-inflammatory activity.

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Supporting Data

Experimental procedure, characterisation data, spectral reports along with docking study table 4 and figures S1-S11 are provided in supporting information file.

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Declaration of interests

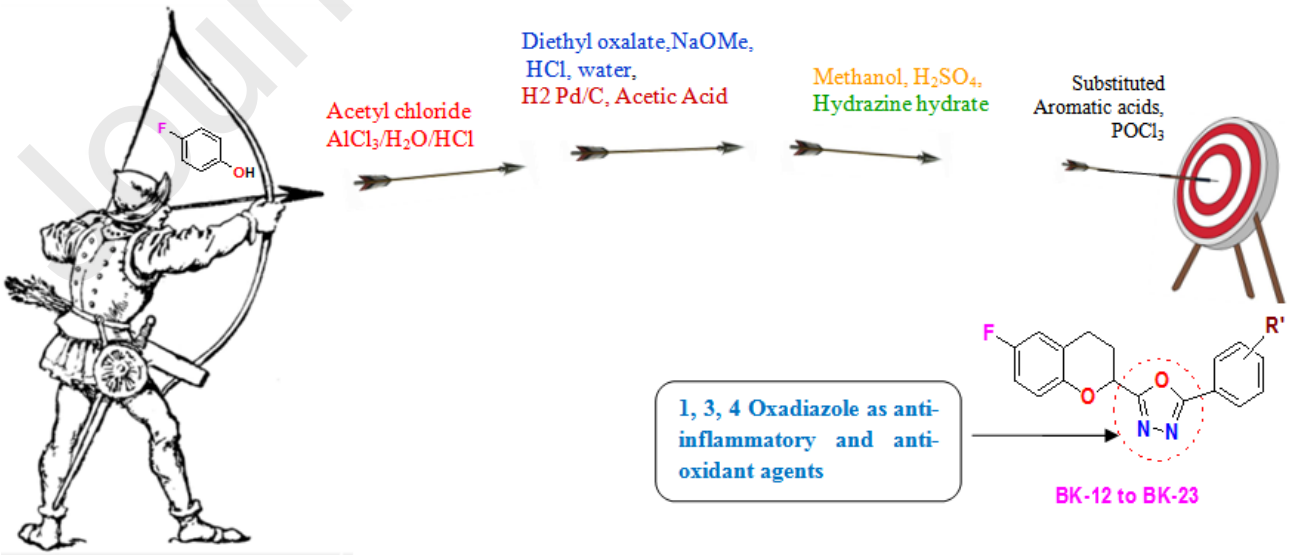
☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

There are no known competing financial interests or personal relationships which may influence the work reported in this paper.

[45]

Graphical Abstract



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