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Research Article

Design of p-methylphenyl Bioisosteres of Celecoxib as Selective COX-II Inhibitors Using Bioisosteric Approach

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Abstract:

In present study, a bioisosteric approach was employed to design analogues of celecoxib, a selective COX-II inhibitor and non-steroidal anti-inflammatory drug. The p-methylphenyl group in celecoxib was targeted for bioisosteric replacement in order to develop newer molecules with reduced adverse effects. A total of 70 p-methylphenyl bioisosteres were generated using the MolOpt tool, including aryl halides, heteroaryl groups, hydrocarbons, and other functional groups. The newly designed analogues were evaluated for their medicinal properties, pharmacokinetic parameters, and toxicity using computational tools such as ADMETLab 2.0 and pkCSM. The results showed that 48 analogues exhibited good drug-likeness based on QED values and all obeys the Lipinski rule, and compound 062 (ethyl 1-(4-sulfamoylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate) was identified as a novel and promising candidate based on its QED and MCE-18 scores. Furthermore, compound 065 (4-[5-(oxan-4-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene-1-sulfonamide) demonstrated lower hepatotoxicity and respiratory toxicity compared to celecoxib. These findings highlight the potential of bioisosteric modifications in designing safer analogues of celecoxib with improved pharmacological properties. Compound 065, in particular, shows promise for further development as a potential anti-inflammatory drug with reduced adverse effects.

Keywords: bioisosteric approach; celecoxib; p-methylphenyl; cox-ii inhibitors; computational tool; molopt

Introduction

Inflammation is a complicated process that happens when tissues are harmed by a variety of things, such as noxious substances (such as bacteria or viruses), physical trauma, toxins, heat, or other causes. There are two main types of inflammation: acute inflammation and chronic inflammation. Acute inflammation is the primary type and acts as the host's essential immune response to remove unwanted stimuli and encourage tissue healing. Acute inflammation is a quick inflammatory response that occurs in the short term. Its goal is to neutralise and eradicate the cause of tissue damage while starting the healing process. Contrarily, chronic inflammation is a response that lasts for weeks, months, or even years. It involves sustained immune cell activation and ongoing production of inflammatory chemicals. Chronic inflammation is frequently accompanied by underlying diseases such autoimmune disorders, recurrent infections, or protracted contact with irritants. The phospholipase A2 pathway is important for the development of inflammation. By preventing the synthesis of leukotrienes and prostaglandins (PGs), two pro-inflammatory chemicals, steroids and nonsteroidal anti-inflammatory medications (NSAIDs) reduce inflammation. These medications block the phospholipase A2 pathway's enzyme activity, which lowers the generation of these inflammatory mediators and reduces inflammation. The cyclooxygenase (COX) enzymes are the molecular targets of all NSAIDs. In several organs, including platelets, kidneys, and the gastrointestinal (GI) tract, COX-1 is a constitutively expressed isoform. It contributes to keeping the GI tract and kidneys in a state of equilibrium.

Chemically, celecoxib is known as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulphonamide. It is an insoluble crystalline powder that dissolves in organic solvents like ethanol and methanol but is almost insoluble in water. Celecoxib has the chemical formula $C_{17}H_{14}F_3N_3O_2S$ and a molecular weight of 381.37 grams per mole. Celecoxib is made up of a pyrazole ring that is joined to a phenyl ring by a sulphonamide group. A trifluoromethyl group (CF_3) and a methyl group (CH_3) are also carried by the phenyl ring in two more

positions. Celecoxib's distinctive pharmacological qualities, such as its selective inhibition of the COX-II enzyme, are a result of these structural characteristics. It is frequently used to treat acute pain, menstrual cramps, and illnesses like arthritis that cause discomfort and inflammation. Celecoxib is a type of COX-II inhibitor that particularly targets the cyclooxygenase-II (COX-II) enzyme, which is necessary for the creation of prostaglandins, which are inflammatory, painful, and fever-inducing chemicals. Celecoxib reduces the generation of prostaglandins that cause inflammation by specifically decreasing COX-II, which lowers pain and swelling. When compared to conventional NSAIDs, celecoxib offers the benefit of having a lower potential for gastrointestinal adverse effects such bleeding and stomach ulcers. This is due to the fact that COX-II inhibitors only target COX-II and spare COX-I, an enzyme that is constitutively produced and necessary for maintaining the stomach and intestines' protective lining. It's crucial to remember that gastrointestinal adverse effects can still happen even with this lower risk, particularly with prolonged or high-dose celecoxib treatment.

Celecoxib has undergone bioisoteric modification. This method substitutes existing groups that produce similar biological properties with substituents or groups with similar chemical or physical properties. The replacement of one or more atoms, groups, or fragments in a molecule with another that has equivalent physical or chemical properties is commonly referred to as a "bioisosteric approach" in drug design. Through structural modification, a drug's biological activity, pharmacokinetics, or physicochemical qualities are intended to be preserved or enhanced. The substituent or group that is switched out during this procedure is referred to as a "bioisostere." Bioisosteric substitutions can be used to achieve a variety of objectives in drug design, including boosting potency, enhancing selectivity, lowering toxicity, boosting metabolic stability, optimising solubility, or modifying other drug-like features. By replacing a specific moiety with a bioisostere, it is possible to maintain the desired interactions with the target biomolecule while altering other aspects of the molecule.

Bioisosteric replacements can be classified into different types based on the nature of the substituent being exchanged. Some common examples include:

- **Classical Bioisosteres:** These involve substituting an atom or group with another that has similar size, shape, and charge distribution. For instance, replacing a hydrogen atom with a halogen atom (e.g., fluorine, chlorine) or an oxygen atom with a sulphur atom.
- **Nonclassical Bioisosteres:** These involve more complex substitutions that may alter the electronic or steric properties of the molecule. Examples include replacing an amide group with an ester, an ester with a carbonate, or an aromatic ring with a bioisosteric heterocycle.

Bioisosteres for Functional Groups: This approach focuses on replacing a specific functional group with another that can mimic its chemical properties. For example, replacing a carboxylic acid (-COOH) with a bioisosteric sulfonic acid (-SO_3H) or a primary amine (-NH_2) with a bioisosteric hydroxamic acid (-C(O)NHOH).

The required pharmacological efficacy, target binding interactions, metabolic pathways, and potential off-target effects must all be carefully taken into account when choosing the right bioisosteres. To aid in the rational design and choice of bioisosteric replacements, computational approaches, structure-activity relationship (SAR) analyses, and medicinal chemistry knowledge are frequently used. The optimisation of drug candidates by adjusting their properties while maintaining the required biological effects is made possible by bioisosteric techniques, which can be useful tools in drug discovery and development. The effective use of bioisosteres, it is crucial to remember, depends on a thorough comprehension of the underlying molecular interactions and possible effects on therapeutic efficacy and safety.

In the current study, the *p*-methylphenyl group in celecoxib molecules has been treated using a bioisosteric technique in order to create newer analogues with less adverse effects, such as liver damage and cardiovascular side effects, which are important contributors to drug withdrawal. Therefore, in order to create comparatively safe molecules, celecoxib *p*-methylphenyl bioisosteres are designed utilising the bioisosteric technique.

Material and Methods

Celecoxib acts as a selective COX-II inhibitor and oral non-steroidal anti-inflammatory drug, it may be hepatotoxic on the long-term use, special precaution may be taken and liver function test is being suggested periodically.

Celecoxib's *p*-methylphenylbioisosteres were designed using MolOpt and the molecular structure of newly designed analogues and their properties is listed in Table 1. Pharmacokinetic and toxicity (ADMET) property of newly designed analogue are envisaged by using ADMETLab 2.0 and pkCSM.

3.1 *p*-methylphenyl Bioisoteres of celecoxib:

MolOpt tool was employed for in-silico design of newer analogues of celecoxib by considering*p*-methylphenylgroup for bioisosteric replacement.

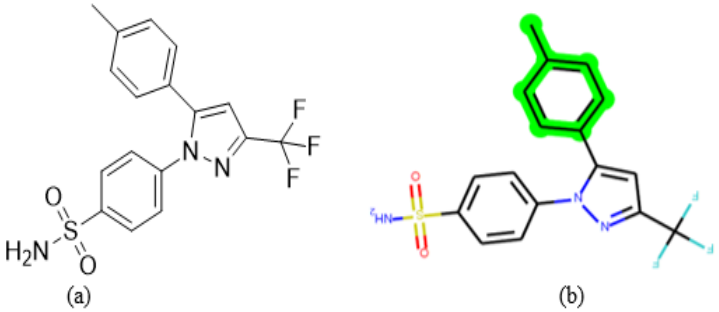


Figure 1: a) Structure of Celecoxib, b) p-methylphenyl group of celecoxib replaced for bioisosteric approach

3.2 Pharmacokinetic and ADMET properties prediction:

Various absorption, distribution, metabolism, excretion and toxicity (ADMET) properties were calculated by using ADMETLab 2.0. In this study, Human Intestinal Absorption property (HIA in %) were calculated by using pkCSM.

Results and Discussion

4.1 Bioisosteres of *p*-methylphenyl group of celecoxib:

Total 70 *p*-methylphenyl bioisosteres analogues of celecoxib were generated i.e., Aryl halide, Aryl and substituted Aryl group, Heteroaryl group, Non aromatic heterocyclic group, Hydrocarbon, Aryl ether, Phenolic, Ester, Alcohol, Halogenated aryl, Cycloalkyl, Amide etc., shown in Figure 2 using MolOpt tool. Bioisosteres and their properties are shown in Table 1.

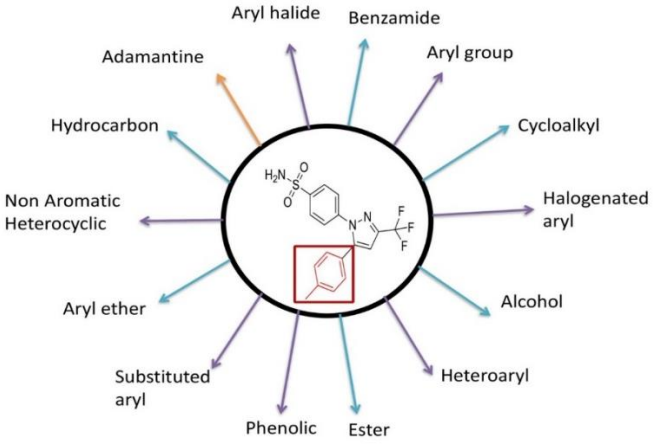
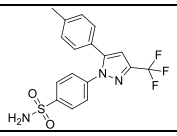
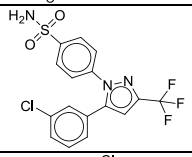
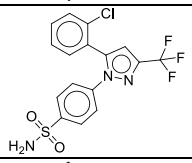
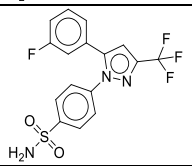
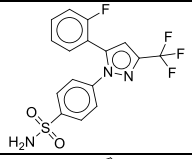
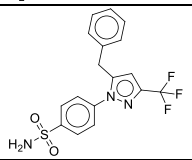
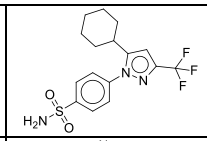
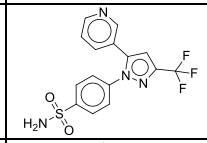
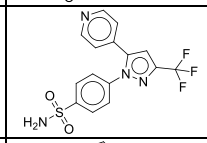
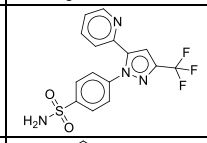
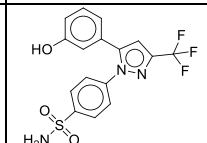
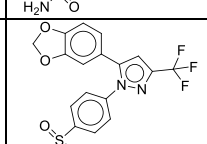
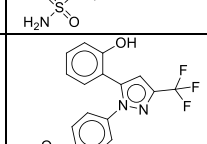
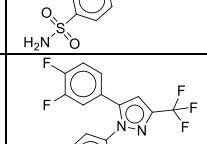
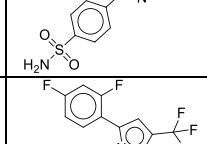
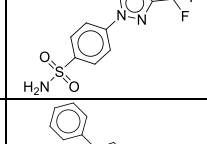
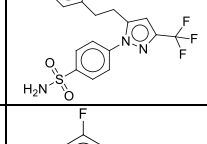
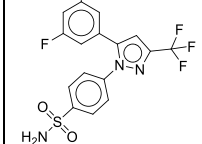
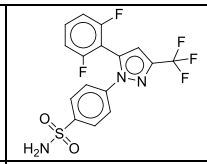
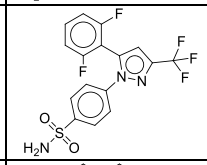
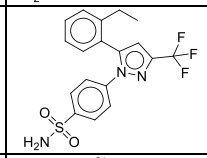
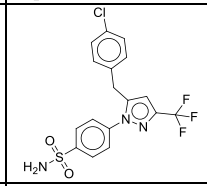
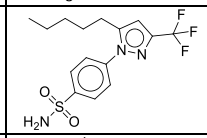
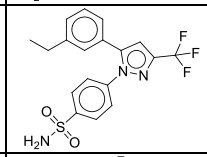
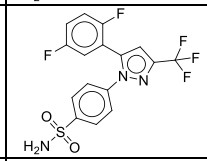
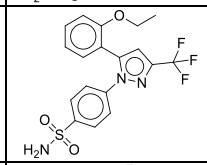
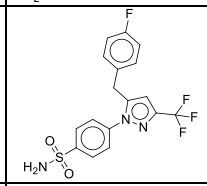
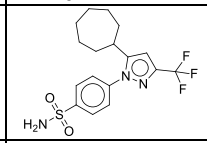
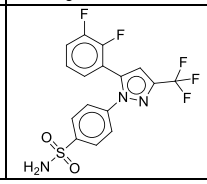
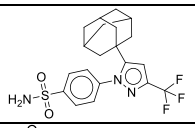
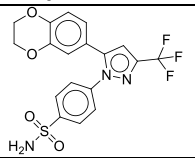
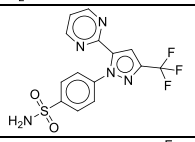
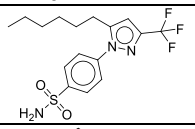
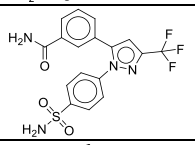
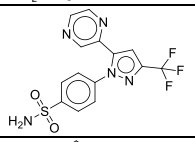
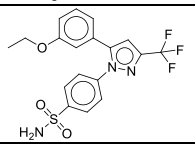
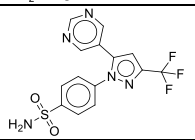
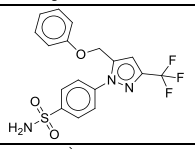
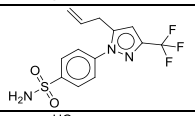
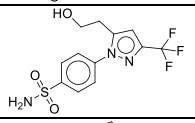
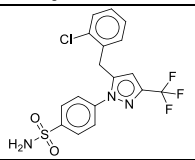
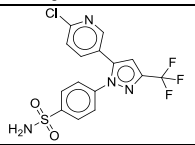


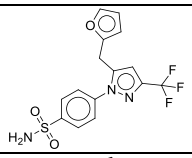
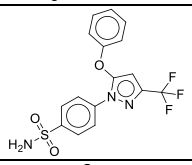
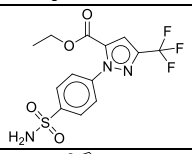
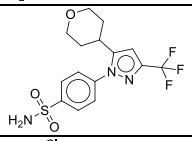
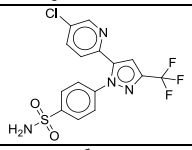
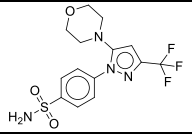
Figure 2: *p*-methylphenyl bioisostere analogues of celecoxib.

S. No	Entry No	Structure	Type of bioisosters	MW	nHA	nHD	nRot	TPSA	LogS	LogP
1.	Celecoxib		*p*-methylphenyl	381.08	5	2	4	77.98	-5.289	3.528
2.	000		Aryl halide	401.02	5	2	4	77.98	-5.594	3.752
3.	001		Aryl halide	401.02	5	2	4	77.98	-5.302	3.441
4.	002		Aryl halide	385.05	5	2	4	77.98	-5.117	3.249
5.	003		Aryl halide	385.05	5	2	4	77.98	-5.01	3.094
6.	005		Benzyl	381.08	5	2	5	77.98	-4.438	3.028

7.	006		Cycloalkyl	373.11	5	2	4	77.98	-5.147	3.586
8.	007		Heteroaryl	368.06	6	2	4	90.87	-3.372	1.977
9.	008		Heteroaryl	368.06	6	2	4	90.87	-3.618	2.062
10.	009		Heteroaryl	368.06	6	2	4	90.87	-4.128	2.213
11.	010		Phenolic	383.06	6	3	4	98.21	-3.949	2.767
12.	011		Heteroaryl	411.05	7	2	4	96.44	-5.423	3.044
13.	013		Phenolic	383.06	6	3	4	98.21	-4.187	2.938
14.	014		Aryl halide	403.04	5	2	4	77.98	-5.432	3.404
15.	015		Aryl halide	403.04	5	2	4	77.98	-5.235	3.215
16.	017		Substituted aryl	395.09	5	2	6	77.98	-4.735	3.32
17.	018		Aryl halide	403.04	5	2	4	77.98	-5.261	3.328
18.	020		Substituted Aryl	393.08	5	2	5	77.98	-4.886	3.53

19.	021		Aryl halide	419.01	5	2	4	77.98	-5.997	3.826
20.	022		Aryl halide	403.04	5	2	4	77.98	-5.608	3.064
21.	023		Substituted Aryl	395.09	5	2	5	77.98	-5.367	3.734
22.	025		Aryl halide	415.04	5	2	5	77.98	-5.092	3.684
23.	027		Hydrocarbon	361.11	5	2	7	77.98	-4.73	3.495
24.	028		Substituted Aryl	395.09	5	2	5	77.98	-5.802	3.89
25.	030		Aryl halide	403.04	5	2	4	77.98	-5.32	3.252
26.	031		Aryl ether	411.09	6	2	6	87.21	-5.03	3.172
27.	032		Halogenated aryl group	399.07	5	2	5	77.98	-4.636	3.12
28.	035		Cycloalkyl	387.12	5	2	4	77.98	-5.55	4.08
29.	036		Aryl halide	403.04	5	2	4	77.98	-5.346	3.252

30.	037		Adamantinyl	425.14	5	2	4	77.98	-5.55	4.329
31.	038		Non-aromatic heterocyclic	425.07	7	2	4	96.44	-5.489	2.965
32.	039		Heteroaryl	369.05	7	2	4	103.76	-3.217	1.044
33.	041		Hydrocarbon	375.12	5	2	8	77.98	-5.124	3.919
34.	042		Benzamide	410.07	7	4	5	121.07	-4.436	2.148
35.	043		Heteroaryl	369.05	7	2	4	103.76	-3.053	1.517
36.	045		Aryl ether	411.09	6	2	6	87.21	-5.303	3.576
37.	049		Heteroaryl	369.05	7	2	4	103.76	-2.955	1.261
38.	051		Aryl ether	397.07	6	2	6	87.21	-4.08	2.535
39.	052		Hydrocarbon	331.06	5	2	5	77.98	-3.396	2.269
40.	054		Alcohol	335.06	6	3	5	98.21	-2.326	0.831
41.	058		Halogenated aryl	415.04	5	2	5	77.98	-4.977	3.714
42.	059		Heteroaryl	402.02	6	2	4	90.87	-4.451	2.658

43.	060		Heteroaryl	371.06	6	2	5	91.12	-3.838	2.419
44.	061		Aryl ether	383.06	6	2	5	87.21	-4.606	2.863
45.	062		Ester	363.05	7	2	6	104.28	-3.493	2.021
46.	065		Non-aromatic heterocyclic	375.09	6	2	4	87.21	-3.513	1.908
47.	067		Heteroaryl	402.02	6	2	4	90.87	-5.119	3.088
48.	069		Non-aromatic heterocyclic	376.08	7	2	4	90.45	-3.876	1.502

MW (Molecular weight), nHA (Number of hydrogen bond acceptor), nHD (Number of hydrogen bond acceptor), nRot (Number of rotatable bonds), TPSA (Topological polar surface area), logP (The logarithm of aqueous solubility value), logS (The logarithm of aqueous solubility value)

Table 1: *p*-methylphenyl bioisostere analogues of celecoxib

4.2 Pharmacokinetic (ADME) and Toxicity properties prediction:

Medicinal properties, Pharmacokinetic properties like absorption, distribution, metabolism, excretion (ADME) and toxicity properties were calculated by using pkCSM and ADMElab2.0. Medicinal Properties of the analogues are shown in Table 2 and among 70*p*-methylphenyl bioisosteres analogues in which all obeys the Lipinski, Pfizer, and golden triangle rule48 compounds showing greater than >0.67 QED value (measure of drug-likeness) indicates that these compounds are attractive but compound 000, 015, 017, 025, 030, 035, 037, 038, 0.45, 058 does not obeys the GSK rule. Compound 006, 011, 035, 037, 038, 065, and 069 having ≥45 MCE-18 score (measure the molecules effectively by novelty in terms of their cumulative sp3 complexity) was found novel, follows the current trend observed in medicinal chemistry.

S. No.	Entry No.	QED	Synth	Fsp3	MCE-18	Lipinski	Pfizer	GSK	Golden Triangle
1.	000	0.723	2.21	0.062	22	Accepted	Accepted	Rejected	Accepted
2.	005	0.754	2.253	0.118	21	Accepted	Accepted	Accepted	Accepted
3.	006	0.893	2.366	0.438	52.957	Accepted	Accepted	Accepted	Accepted
4.	011	0.715	2.375	0.118	54.737	Accepted	Accepted	Rejected	Accepted
5.	013	0.727	2.299	0.062	22	Accepted	Accepted	Accepted	Accepted
6.	015	0.68	2.33	0.062	23	Accepted	Accepted	Rejected	Accepted
7.	017	0.72	2.242	0.167	21	Accepted	Accepted	Accepted	Accepted
8.	025	0.704	2.319	0.118	22	Accepted	Accepted	Rejected	Accepted
9.	027	0.802	2.322	0.4	17	Accepted	Accepted	Accepted	Accepted
10.	028	0.731	2.24	0.167	22	Accepted	Accepted	Accepted	Accepted
11.	030	0.68	2.346	0.062	23	Accepted	Accepted	Rejected	Accepted
12.	032	0.684	2.324	0.118	22	Accepted	Accepted	Accepted	Accepted
13.	035	0.81	2.371	0.471	53.76	Accepted	Accepted	Rejected	Accepted
14.	037	0.807	3.88	0.55	84.645	Accepted	Accepted	Rejected	Accepted
15.	038	0.696	2.404	0.167	56.952	Accepted	Accepted	Rejected	Accepted
16.	041	0.75	2.331	0.438	17	Accepted	Accepted	Accepted	Accepted
17.	044	0.707	2.291	0.118	22	Accepted	Accepted	Accepted	Accepted
18.	045	0.695	2.241	0.167	22	Accepted	Accepted	Rejected	Accepted
19.	051	0.717	2.228	0.118	21	Accepted	Accepted	Accepted	Accepted

20.	054	0.873	2.418	0.25	17	Accepted	Accepted	Accepted	Accepted
21.	058	0.704	2.376	0.118	22	Accepted	Accepted	Rejected	Accepted
22.	060	0.763	2.561	0.133	21	Accepted	Accepted	Accepted	Accepted
23.	062	0.833	2.26	0.231	18	Accepted	Accepted	Accepted	Accepted
24.	065	0.893	2.513	0.4	52	Accepted	Accepted	Accepted	Accepted
25.	069	0.874	2.457	0.357	50.842	Accepted	Accepted	Accepted	Accepted
26.	Celecoxib	0.754	2.144	0.118	22	Accepted	Accepted	Accepted	Accepted

QED (A measure of drug-likeness based on the concept of desirability), SAscore (Synthetic accessibility score), Fsp3 (The number of sp3 hybridized carbons/total carbon count), MCE-18 (Medicinal chemistry evolution in 2018).

Table 2: Medicinal Properties of selected Analogues

Compound having value more than >0.7 indicating toxicity like hepatotoxicity (H-HT), cardiovascular toxicity (hERG), and respiratory toxicity was not included in the Table 3-5. Absorption properties (Caco-2, MDCK, and HIA) and distribution properties (Plasma Protein Binding, Volume of Distribution, Blood-Brain Barrier and Fu) are shown in Table-3. All the analogues have proper caco-2 permeability, high passive MDCK permeability and human intestinal absorption more than 90%, indicating that these compounds may be orally effective. Human Intestinal Absorption property (HIA in %) was calculated by using pkCSM, shown in Table 3.

S. No.	Entry No.	Caco-2	MDCK	HIA (%)	BBB	PPB	VDss
1.	000	-4.72	1.76E-05	91.511	0.503	96.22%	1.382
2.	005	-4.838	3.38E-05	91.976	0.702	93.12%	0.955
3.	013	-4.98	1.90E-05	93.182	0.17	94.27%	0.955
4.	015	-4.645	2.74E-05	91.598	0.412	94.30%	0.906
5.	017	-4.774	2.17E-05	93.088	0.793	94.88%	1.128
6.	025	-4.782	2.24E-05	92.152	0.502	95.95%	0.923
7.	027	-4.689	2.97E-05	91.084	0.839	92.00%	2.031
8.	028	-4.679	2.24E-05	92.742	0.563	95.38%	1.4
9.	030	-4.649	2.77E-05	92.763	0.37	94.57%	0.859
10.	032	-4.802	3.23E-05	93.248	0.495	94.43%	0.844
11.	041	-4.71	2.68E-05	90.728	0.805	94.18%	2.136
12.	044	-5.045	1.57E-05	94.951	0.774	84.23%	1.179
13.	045	-4.758	2.10E-05	92.718	0.297	95.51%	1.421
14.	051	-4.941	2.93E-05	91.41	0.401	94.94%	1.197
15.	054	-4.866	2.38E-05	81.173	0.979	44.57%	1.354
16.	058	-4.737	3.65E-05	92.923	0.686	95.87%	0.999
17.	060	-4.849	3.21E-05	94.991	0.544	87.34%	1.047
18.	062	-4.939	3.38E-05	83.669	0.858	81.65%	0.866
19.	065	-4.873	2.67E-05	93.407	0.895	63.82%	1.41
20.	Celecoxib	-4.767	2.30E-05	92.995	0.586	94.96%	1.105

Caco-2 (The human colon adenocarcinoma cell lines), MDCK (Madin−Darby Canine Kidney cells) and >2 x 10-6cm/s indicates excellent, HIA (Human Intestinal Absorption), (PPB) Plasma protein binding, BBB (blood–brain barrier), VD (Volume Distribution), Fu (The fraction unbound in plasms).*Property calculated by pkCSM.

Table 3: Absorption and Distribution Profile of the selected Analogues

Metabolism (CYP1A2-inh and sub, CYP2C19-inh and sub, CYP2C9-inh and sub, CYP2D6-inh and sub, CYP3A4-inh and sub) were calculated by using pkCSM and excretion (CL and T1/2) properties are shown in Table-4 and compounds having value <5 showing low clearance.

S. No.	Entry No.	CYP1A2	CYP2C9	CYP2D6	CYP3A4	CL	T1/2
1.	000	YES	YES	NO	NO	1.034	0.027
2.	005	YES	NO	NO	NO	1.115	0.07
3.	013	YES	YES	NO	YES	0.959	0.049
4.	015	YES	YES	NO	YES	1.242	0.014
5.	017	NO	YES	NO	YES	1.06	0.042
6.	025	YES	YES	NO	YES	1.379	0.037
7.	027	YES	YES	NO	NO	1.315	0.043
8.	028	YES	YES	NO	YES	0.958	0.039
9.	030	YES	YES	NO	NO	1.245	0.014
10.	032	YES	YES	NO	YES	1.309	0.032
11.	041	YES	YES	NO	NO	1.342	0.036
12.	044	YES	NO	NO	YES	0.93	0.101
13.	045	YES	YES	NO	YES	1.161	0.03
14.	051	NO	YES	NO	NO	1.019	0.077

15.	054	NO	NO	NO	NO	1.28	0.169
16.	058	YES	YES	NO	YES	1.553	0.036
17.	060	YES	NO	NO	NO	1.163	0.095
18.	062	YES	NO	NO	NO	1.401	0.051
19.	065	NO	NO	NO	NO	1.123	0.048
20.	Celecoxib	YES	YES	NO	YES	0.992	0.029

Human cytochrome P450 (five isozymes—1A2, 3A4, 2C9, 2C19 and 2D6), CL (The clearance of a drug), T1/2 (The half-life of a drug)

Table 4: Metabolism and Excretion Profile of selected Analogues

Toxicity profile (hERG, H-HT, DILI, Ames, ROA, Carcinogenicity, Respiratory toxicity) of selected analogue are shown in Table 5 and compound 062 are found less hepatotoxic and compound 005, 017, 025, 032, 051, 054, 058, 062 are found less respiratory toxic which is the common reason of market withdrawal of drugs. According to this data the compound 062 are less hepatotoxic and respiratory toxic than the lead compound.

S. No.	Entry No.	hERG	H-HT	DILI	Ames	ROA	Carcinogenicity	Respiratory toxicity
1.	000	0.174	0.615	0.991	0.009	0.73	0.088	0.582
2.	005	0.053	0.466	0.992	0.025	0.476	0.127	0.211
3.	013	0.03	0.552	0.992	0.025	0.741	0.127	0.655
4.	015	0.134	0.698	0.991	0.025	0.671	0.169	0.663
5.	017	0.156	0.64	0.988	0.023	0.722	0.117	0.154
6.	025	0.117	0.467	0.992	0.016	0.497	0.129	0.147
7.	027	0.06	0.393	0.989	0.011	0.604	0.084	0.635
8.	028	0.204	0.588	0.99	0.014	0.729	0.078	0.53
9.	030	0.165	0.683	0.99	0.02	0.665	0.146	0.644
10.	032	0.101	0.48	0.992	0.027	0.337	0.185	0.267
11.	041	0.071	0.383	0.988	0.011	0.581	0.085	0.698
12.	044	0.107	0.436	0.992	0.013	0.702	0.066	0.344
13.	045	0.165	0.491	0.991	0.017	0.557	0.12	0.408
14.	051	0.094	0.6	0.993	0.037	0.578	0.268	0.27
15.	054	0.029	0.443	0.991	0.019	0.568	0.114	0.186
16.	058	0.051	0.637	0.993	0.016	0.589	0.138	0.222
17.	060	0.042	0.405	0.991	0.02	0.645	0.166	0.376
18.	062	0.031	0.109	0.991	0.006	0.453	0.088	0.258
19.	065	0.146	0.663	0.989	0.037	0.934	0.248	0.424
20.	Celecoxib	0.105	0.641	0.991	0.016	0.771	0.139	0.584

H-HT (The human hepatotoxicity), DILI (Drug-induced liver injury), hERG Blockers (Human ether-a-go-go related gene), Ames (test for mutagenicity), ROA (Rat Oral Acute Toxicity)

Table 5: Toxicity Profile of selected Analogues

Conclusion:

Many of the celecoxib analogues were designed using bioisosteric approach and their medicinal, pharmacokinetic and toxicity properties were calculated by using in-silico methods. The results indicate 70 analogues are generated by the *p*-methylphenyl celecoxib bioisosteres as anti-inflammatory drug. Each analogue was evaluated based on QED value (eight physicochemical properties, including MW, log P, HBA, HBA, PSA, number of rotatable bonds, number of aromatic rings, and the presence of undesirable functional groups) and 48 analogues were selected having QED values of 0.67 or greater, indicating good drug-like properties. The compound 062 (ethyl 1-(4-sulfamoylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate) was found novel based on QED and MCE-18 score, follows the current trend observed in medicinal chemistry and one of the analogue compounds 065 (4-[5-(oxan-4-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene-1-sulfonamide) found to have low hepatotoxicity and respiratory toxicity compared to celecoxib, making it a promising candidate for further development.

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