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QSAR/QSPR: Designing of new non-steroidal anti- inflammatory drugs (NSAIDs) considering ibuprofen as a lead compound followed by their synthesis and evaluation

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ABSTRACT

Computer-aided Drug Discovery and Development (CADD) is used for virtual screening of various compounds to discover a new drug. In this way five novel anti-inflammatory drugs are selected by virtual screening and they are only synthesized. Further, these novel NSAIDs are evaluated and found to have comparable anti-inflammatory activity to Ibuprofen.

Keywords: CADD, virtual screening, Ibuprofen analogues, NSAIDs

INTRODUCTION

Use of computational techniques in drug discovery and development process is rapidly gaining popularity, implementation and appreciation. Term Computer-Aided Drug Discovery and Development (CADD)[1] will be employed to cover the entire process. Both computational and experimental techniques have important roles in drug discovery and development and CADD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (pharmacokinetic) properties. Virtual screening is used to discover new drug candidates from different structure scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases. It is intended to reduce the size of chemical space and thereby allow focus on more promising candidates for lead discovery and optimization. The goal is to enrich set of molecules with desirable properties (active, drug-like, lead-like) and eliminate compounds with undesirable properties (inactive, reactive, toxic, poor ADMET/PK). In other words, in-silico modeling is used to significantly minimize time and resource requirements of chemical synthesis and biological testing[2]. Role of computational models is to increase prediction based on existing knowledge[3]. Computational methods are playing increasingly larger and more important role in drug discovery and development. In early 1960s, Corwin. Hansch[4] extended the concept of Linear-free energy relationship (LFER) to describe the effectiveness of biologically-active molecule. Generating useful Hansch equation can be very challenging and even a good Hansch equation will not give perfect prediction of activity. For this reason new methods have somewhat replaced the traditional Hansch analysis. In the late 1980s and early 1990s combinatorial chemistry emergent molecular field Analysis (COMFA)[5] has emerged. This method uses highly complicated statistical analysis with large number of variables to correlate practical molecular properties to activity. However, drug designing is still a challenge. We wish to report a simple hypothesis, in which series of derivatives of Ibuprofen (known non-steroidal anti-inflammatory drugs) were

designed and different physicochemical properties were calculated such as log P, H-Donor, H-Acceptor, molecular weight and pka. And their physicochemical properties are compared with Ibuprofen. All the new non-steroidal anti-inflammatory drugs (NSAID) selected for designing have to follow Lipinski's Rule of Five [6], in general, an orally active drug has no more than violation of the following criteria:

Not more than five hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms) not more than ten hydrogen bond acceptors (nitrogen or oxygen atoms) A molecular mass less than five hundreds Daltons. An octanol-water partition coefficient log P not greater than 5. Note that all numbers are multiples of five, which calculated five compounds having similar physicochemical properties as lead compounds were selected for synthesis. They were found to have potential anti-inflammatory activity.

MATERIALS AND METHODS

Material:

All reagents were purchased from Merck and Loba and used without further purification. Melting points were measured in open capillary and are uncorrected. The products were characterized by IR, ¹H NMR was recorded on Bruker MSL-300 instrument using TMS as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX.

Methods:

General Procedure for the preparation of methyl ester of various α -aryl propanoic acids:

Methyl esters of α -aryl propanoic acids were synthesized using direct esterification method. α -aryl propanoic acid (0.004 mols) and methyl alcohol (0.25 mols) were taken in round bottom flask fitted with reflux condenser. Sulphuric acid (conc., 1ml) was added gradually to this reaction mixture. The reaction mixture was refluxed with continuous stirring at 80°C for 6 hrs to complete the esterification (confirmed by TLC). After completion of reaction the excess alcohol was removed by distillation under reduced pressure. Crude product was dissolved in dichloromethane (30ml) and was washed with aq. sodium bi-carbonate solution (10%, 30 ml) and organic layer was dried over anhydrous sodium sulphate followed by filtration. Solvent was removed under vacuum to furnish the crude product, which was purified by column chromatography on SiO₂ using 5% ethyl acetate in pet ether as an eluent [7].

General procedure for α -halogenation of methyl ester of various α -aryl propanoic acids followed by hydrolysis:

The ester (0.01mmol), N-halosuccinamide (0.014mmol) and AIBN (0.03gm) were taken in CCl₄ (25ml) and resulting reaction mixture was refluxed till the completion reaction, (monitored by TLC). After completion of the reaction solution was cooled to ambient temperature. The crystals of succinamide were removed by filtering through small celite column. Solvent was evaporated under vacuum and crude halogenated product was collected. This crude halogenated product and NaOH (10% 20ml) was stirred at 80°C for two hours. The reaction mixture was cooled to ambient temperature and acidified with conc. HCL and extracted by ether (20ml). The ether layer was washed with water (20×30ml) followed by brine and dried over anhydrous sodium sulphate. Ether was evaporated under vacuum to furnish corresponding acid as a viscous liquid.

Carrageenan-induced paw edema:

To assess the activity of the designed compounds, selected analogs compounds namely 2,3,4,5 and 21 were evaluated by screening protocol: namely, the indomethacin and carrageenan-induced paw edema and turpentine oil-induced granuloma pouch bioassays, using indomethacin (10mg/kg) as a reference standard anti-inflammatory agent. The paw edema [8] was employed as a model for acute and sub-acute inflammation condition. The data obtained are presented in the following table and expressed as means $\pm$ SE. Statistical differences of control and test groups was carried out using the Analysis of Variance (ANOVA). The difference in results was considered significant when $P < 0.05$.

RESULTS AND DISCUSSION

From the various newly designed compounds only for twenty two compounds (Fig.1), various physical properties and molecular descriptors like log P, pka are calculated by using different software such as Vega zz, Mopac, and Chem Draw etc. and they are compared with the lead compound Ibuprofen. The results are shown in the table 1

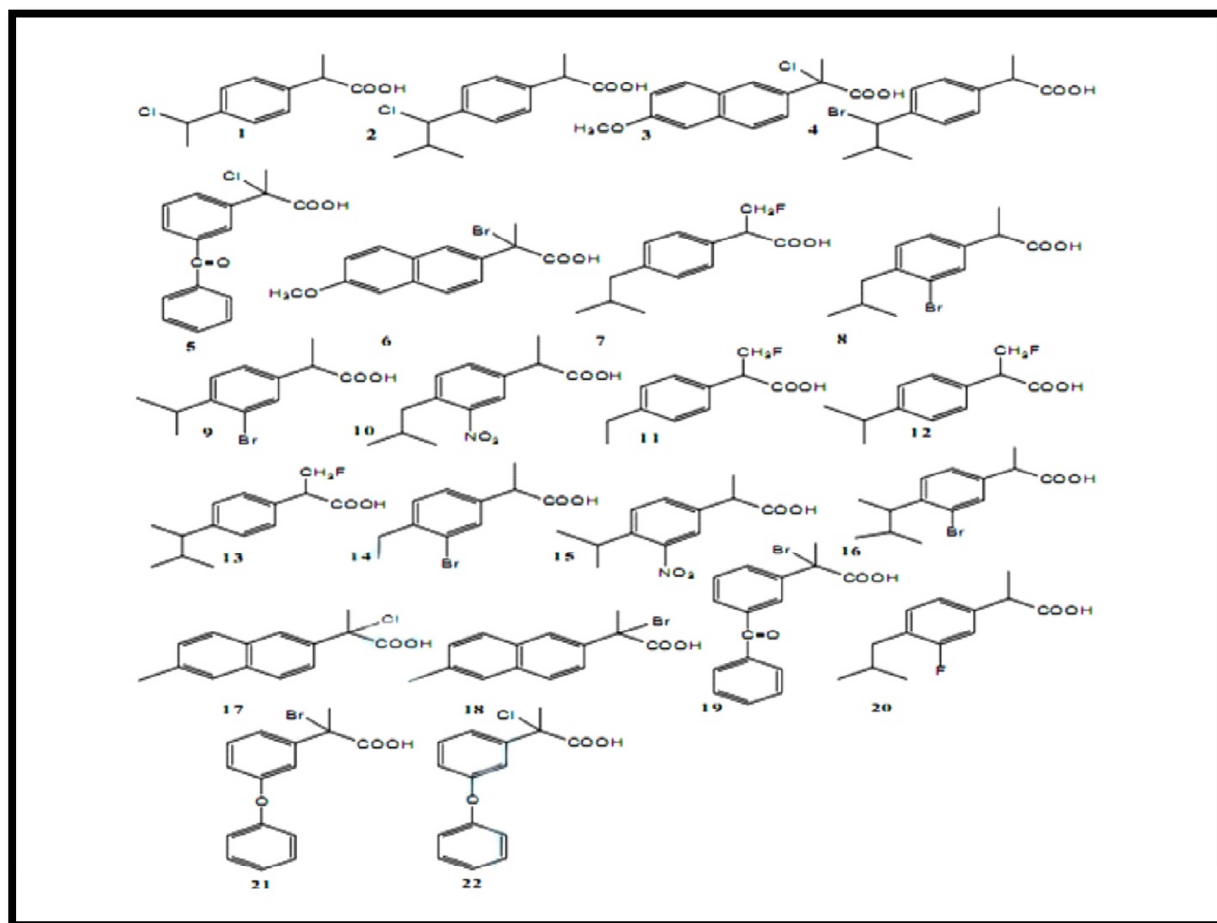


Fig.1: The structure of lead compounds

Table1: Calculated values of physical properties such as H.F, D>M HUMO, and LUMO etc

Derivatives	M.W	H.F(ev)	D.M(D)	HOMO	LUMO	H.D	H.A	Log P	pKa
Ibuprofen	206.2	-447	1.56	-9.472	4.07	1	4	3.72	4.30
Naproxen	230.2	-380	1.38	-9.371	0.69	1	4	2.97	4.19
Ketoprofen	254.2	-380	1.61	-9.762	1.66	1	5	3.31	3.88
Fenoprofen	242.2	-379	2.04	-9.532	0.87	1	3	3.64	3.96
1	212.6	-421	3.51	-9.654	0.18	1	4	3.07	4.38
2	240.7	-468	3.37	-9.650	0.10	1	4	3.69	4.56
3	264.7	-434	1.07	-8.775	0.76	1	5	3.37	3.79
4	285.1	-426	2.28	-9.594	5.81	1	4	4.08	3.97
5	288.7	-399	0.93	-10.028	0.57	1	6	3.71	3.58
6	309.1	-392	1.76	-8.612	0.69	1	5	3.49	3.06
7	224.2	-643	1.54	-9.470	0.33	1	4	3.40	4.79
8	285.1	-432	2.45	-7.791	5.24	1	4	4.58	3.76
9	271.1	-411	2.48	-9.596	1.07	1	4	4.17	3.66
10	251.2	-395	4.36	-7.676	0.37	1	7	3.10	3.72
11	196.2	-596	1.46	-9.527	0.30	1	4	2.65	4.64
12	210.2	-622	1.53	-9.530	0.31	1	4	2.98	4.72
13	238.2	-669	1.54	-9.642	0.15	1	4	3.73	4.85
14	257.1	-386	2.47	-9.602	8.10	1	4	3.84	3.57
15	237.2	-377	4.39	-9.546	1.23	1	7	2.65	3.62
16	299.2	-458	2.50	-7.682	7.55	1	4	4.91	3.83
17	248.7	-353	1.86	-8.653	0.62	1	4	3.68	4.29
18	293.1	-260	2.85	-8.637	0.63	1	4	4.10	3.52
19	333.1	-357	2.66	-9.999	0.57	1	6	3.83	2.86

20	224.2	-655	2.38	09.536	5.84	1	4	3.91	4.42
21	321.1	-356	2.22	-9.016	0.33	1	4	3.15	2.90
22	276.7	-389	1.52	-8.683	0.55	1	4	4.04	3.62

*M.W: Molecular Weight *H.F: Heat of formation *D>M: Dipole Moment
 *HOMO,LUMO: High Occupied/Low unoccupied Molecular Orbital *H.D/HA:Hydrogen Donor/Acceptor

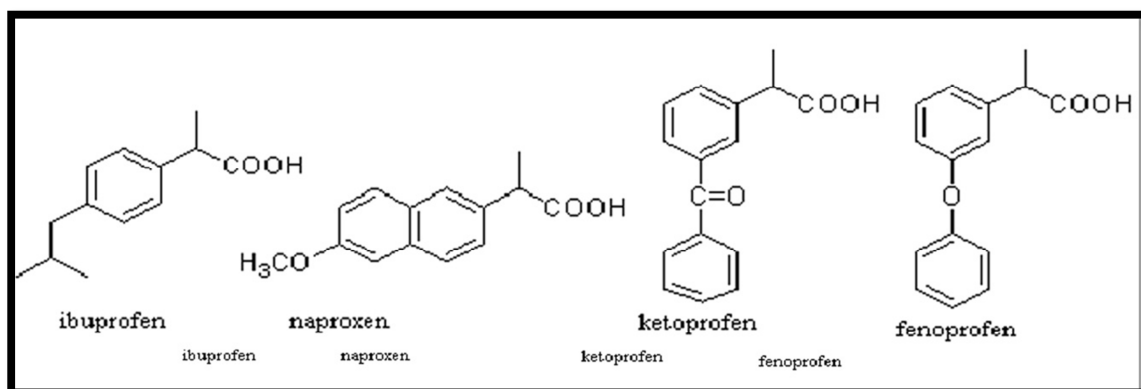
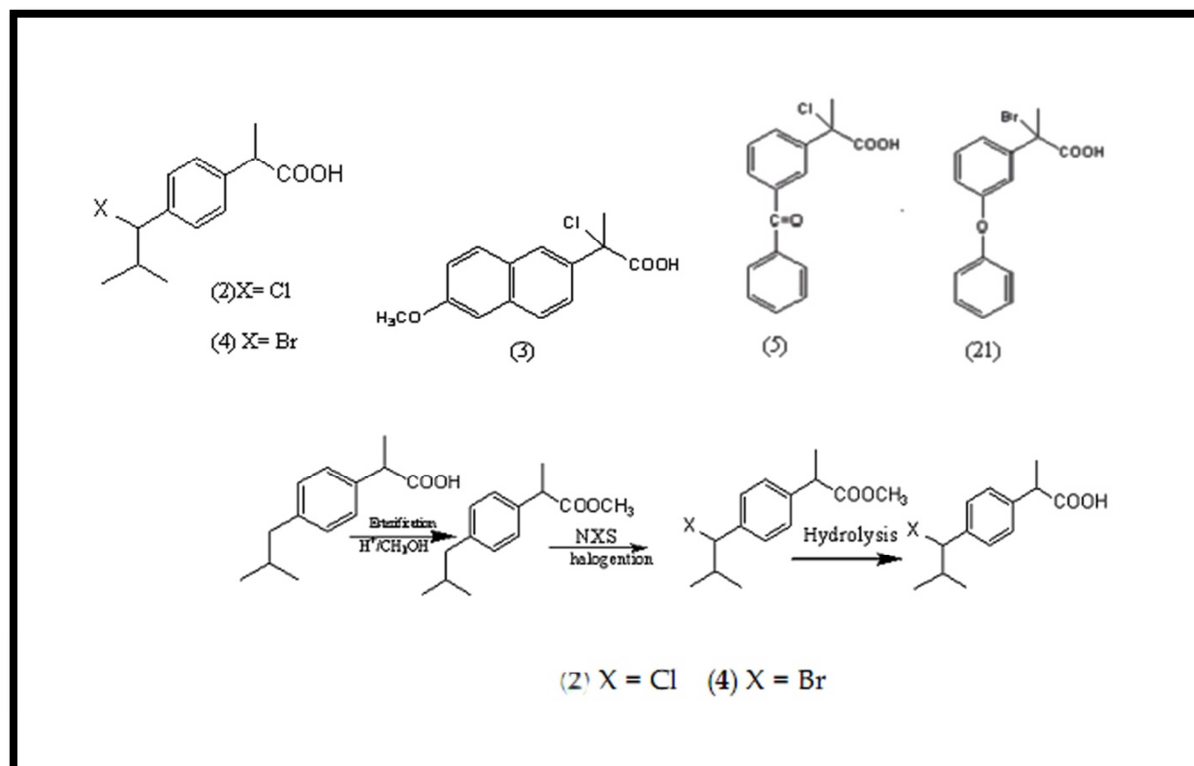
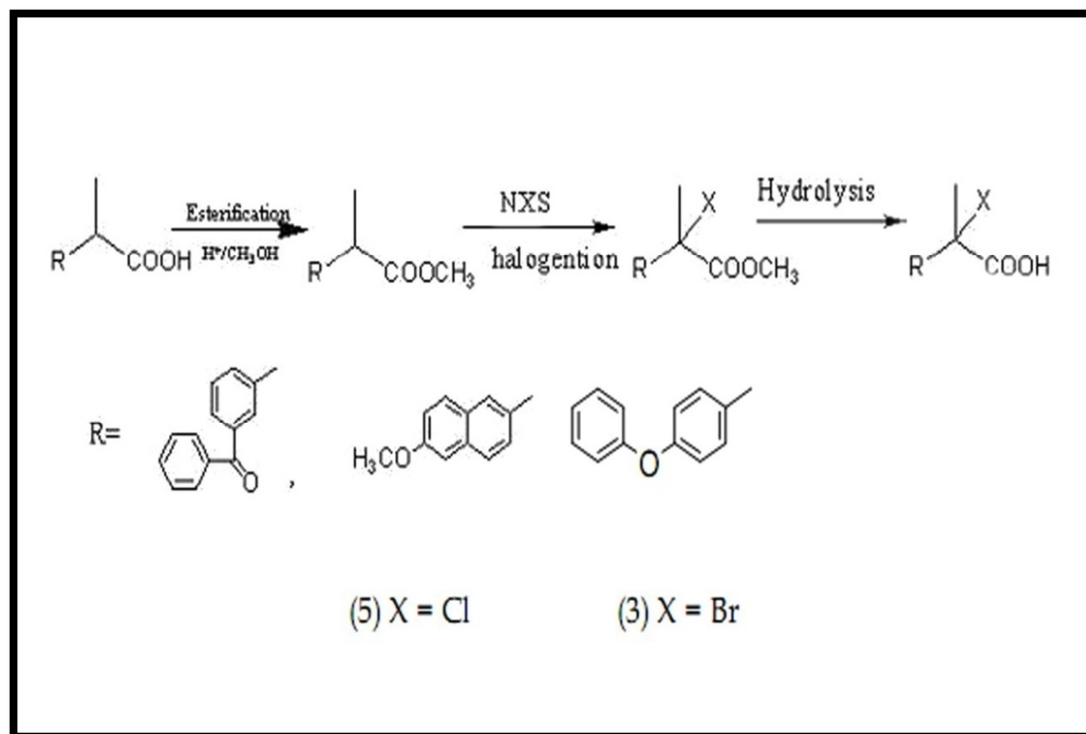


Fig. 2: The selected compounds

Based on the properties α -aryl propanoic acid derivatives 2,3,4,5 and 21 selected for their synthesis are shown below;



Scheme I: Synthesis 2 and 4



Scheme II: Synthesis of compound 21

Direct esterification[9] of Ibuprofen, Naproxen[10], and Ketoprofen [11] was accomplished by using corresponding alcohol in presence of conc. H_2SO_4 as catalyst. After ester was halogenated[12] in case of ibuprofen halogenations took place at isobutyl position rather than α -position to $\text{C}=\text{O}$ this may be due to steric hindrance than the corresponding halogenated ester was hydrolyzed to get the α -(p-chloro/ p-bromo isobutyl phenyl propanoic acid). However in case of ketoprofen and Naproxen ester

α -halogenations took place α -position to $\text{C}=\text{O}$. Since fenopropfen was not available easily so it was decided to prepare in the laboratory by following reported procedure[13] The reaction is depicted in scheme VI followed by halogenations to get the α -bromo ester and this was hydrolyzed to (α -bromo α -m-phenoxyphenyl propanoic acid). The structures of all the compounds were confirmed by IR, NMR and Mass spectra. All these new five compounds α -aryl propanoic acid derivatives were selected for their synthesis as depicted in Scheme I & II and their structures were confirmed using infrared, ^1H NMR, spectroscopy and Mass Spectrometry.

Anti-inflammatory Activity:

Table:2 Effect of various synthesized compounds on carrageenan-induced paw oedema in Rats in different time intervals

Treatment and Dose	Mean paw Oedema Volume (100mg/ml)			
	0h	1h	2h	3h
Std. Indomethacin	3.84 ± 0.36**	4.14 ± 0.2**	3.65 ± 0.21**	3.46 ± 0.23**
Ibuprofen	3.78 ± 0.02**	5.01 ± 0.11**	3.12 ± 0.21**	3.02 ± 0.20**
2	3.58 ± 0.02**	5.01 ± 0.11**	3.10 ± 0.29**	3.53 ± 0.06**
3	4.27 ± 0.25**	4.73 ± 0.13**	4.51 ± 0.10**	4.31 ± 0.08**
4	3.74 ± 0.07**	4.23 ± 0.13**	4.22 ± 0.13**	3.99 ± 0.04**
5	3.89 ± 0.03**	3.51 ± 0.10**	5.10 ± 0.18**	4.21 ± 0.10**
21	3.68 ± 0.84**	4.76 ± 0.36**	5.15 ± 0.21**	4.50 ± 0.11**

** $p < 0.05$, SEM = Standard error to mean.

CHARACTERIZATION

Methyl 2- (4-isobutylphenyl) propanoate : Yellowish brown viscous liquid, Yield: 82%; IR(KBr) cm^{-1} : 2974, 2935, 1736, 1605, 1445, 1331, 1267, 1227, 1177, 1028, 858, 821, 685.; $^1\text{H NMR}$ (δ ppmm): 1.6(d,3H), 3.7(s,3H), 3.8(q,1,H), 3.9(s,3H), 7.1 to 7.8 (m,6H)

2-(3-benzoylphenyl) methyl propanoate Yellowish brown viscous liquid yield 80%; IR(KBr) cm^{-1} : 3032, 2953, 1732, 1603, 1497, 1454, 1435, 1344, 1257, 1161, 1012, 751, 725.; $^1\text{H NMR}$ (δ ppm): 1.5(d,3H), 3.53(s,3H), 3.73(q,1H), 7.4 to 7.8(m, 9H)

Methyl 2(3-phenoxoyphenyl) propoanoate : Yellowish brown viscous liquid yield 70%; IR(KBr) cm^{-1} : 2980, 2940, 1740, 1590, 1500, 1460, 1250, 1170, 1080, 930, 700.; $^1\text{H NMR}$ (δ ppm): 1.40(d,3H), 3.68(s,3H), 3.88(q,1H), 6.80 to 7.56(m,9H)

2-(p-chloroisobutyl phenyl) propanoic acid: IR(KBr) cm^{-1} : 3088 to 2874 (board), 1707, 1661, 1512, 1460, 1413, 1377, 1286, 1230, 1068, 908, 858, 734.; $^1\text{H NMR}$ (δ ppm): 0.9(d,6H), 1.5(d,3H), 1.85(m,1H); 2.5(d,1H), 3.7(q,1H), 7.15(d,2H), 7.25; (d,2H), 9.72, (broad s, 1H). $\text{M}+240, 242$ ($\sim 3:1$) for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{Cl}$

2-chloro-2(2-methoxynaphthalen-6-yl) propanoic acid: IR(KBr) cm^{-1} : 3300 to 2900(broads, 1720, 1600, 1497, 1450, 1379, 1356, 1273, 1151, 1069, 974, 798.; $^1\text{H NMR}$ (δ ppm): 1.6(s,3H), 3.7(s,3H), 6.4 to 8.1(d,4H), 2.3(broad s, 1H) $\text{M} = 264, 266$ ($\sim 3:1$) $\text{C}_{14}\text{H}_{13}\text{O}_3\text{Cl}$

2-(p-bromoisobutyl phenyl) propanoic acid: IR (KBr) cm^{-1} : 3088 to 2872 (broad), 1707, 1612, 1512, 1460, 1415, 1381, 1228, 1177, 1074, 935, 860, 792. $^1\text{H NMR}$ (δ ppm): 0.9(d,6H), 1.9(m,1H), 2.45(d,1H), 3.7(m,1H), 7.1 to 7.45 (m,4H), 9.57 (broad s, 1H). $\text{M}+284, 286$ ($\sim 1:1$) for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{Br}$.

2-(3-benzoylphenyl) 2-chloropropanoic acid : IR (KBr) cm^{-1} : 3300 to 2900 (broad), 1711, 1462, 1377, 1292, 1159, 1109, 721. $^1\text{H NMR}$ (δ ppm): 2.31 (s,3H), 7.25 to 7.95 (m, 9H), 7.57(bpard s, 1H). $\text{M}+ 288, 290$ ($\sim 3:1$) for $\text{C}_{16}\text{H}_{13}\text{O}_3\text{Cl}$

2-(3phenoxyphenyl) 2 bromopropainoic acid : IR (KBr) cm^{-1} : 3392 to 299 (board), 1710 1585, 1465, 1379, 1254, 1217, 1163, 970, 820, 759. $^1\text{H NMR}$ (δ ppm): 1.85(s,3H), 4.7(broad s, 1H), 6.9 to 7.45 (m,9H). $\text{M}+ 320, 322$ ($\sim 1:1$) for $\text{C}_{15}\text{H}_{13}\text{O}_3\text{Br}$.

CONCLUSION

Design in-silico filters to eliminate compounds with undesirable properties poor activity and select the most promising candidates. Computer-Aided Drug, Discovery And Development (CADD) is used for virtual screening of various compounds to discover a new drug. In this way five novels anti-inflammatory drug are selected by virtual screening and they are only synthesized. Further, these novel NSAIDs are evaluated and found to have comparable anti-inflammatory activity to Ibuprofen.

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