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Original Research Article

Influence of Derivatization on Molecular and Pharmacokinetic Properties of Phenoxy Acids – An *In Silico* Study

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Abstract: Molecular and pharmacokinetic properties prediction is important determinant in the current drug development process. In this study, molecular and pharmacokinetic properties of phenoxy acids and their derivatives are theoretically predicted using *in silico* tools to determine how synthetic modifications such as branching, amidation, esterification, heterocyclic groups, and hydrazide group change the structural and pharmacokinetic properties with respect to the parent phenoxy acid. From the results it was observed that phenoxy acid possess good central nervous system (CNS) permeability compared to the acid derivatives. It could also be further predicted that conversion of phenoxy acid to functional derivatives leads to molecules with good pharmacokinetic profile. Based upon these theoretical predictions, it can be concluded that various chemical modifications of phenoxy acid moiety furnish promising derivatives with good pharmacokinetic profile and oral bioavailability.
Keywords: Phenoxy acids, preADME, Molinspiration

INTRODUCTION

In the current drug development process molecular modelling techniques are extensively used in order to persuade that the lead structure contains optimum absorption, distribution, metabolism and excretion (ADME) properties [1]. The aim of *in silico* studies is to select molecules with suitable properties and to eliminate compounds with undesirable properties. Computational chemistry resources (online) have been widely used to study molecular properties lipophilicity, topological surface area, molecular weight, sum of hydrogen bond acceptors and donors, number of violations, number of rotatable bonds and molecular volume to assess oral bioavailability and ADME profile of ligand molecules such as Caco2 cell (human epithelial colorectal adenocarcinoma cells) and MDCK (Madin-Darby Canine Kidney Epithelial Cells) cell permeability, skin permeability, plasma protein binding (PPB), and blood brain barrier penetration (BBB) to predict their pharmacokinetic behaviour [2-3].

Phenoxy acids and their derivatives are associated with wide variety of pharmacological activities such as anti hyperlipidemic, hypoglycaemic, antimicrobial, antiviral, antitubercular, antiinflammatory, analgesic, anticancer, antioxidant, and antihypertensive activities. Phenoxy propionic acid moiety is a part of hypolipidemic agents, fenofibrate and gemfibrozil (Fig: 1 and 2) [4].

Significance of carboxylic acid (-COOH) functional group

In general, introduction of carboxylic acid moiety increases water solubility of lead molecule which leads to enhancement of the absorption into the biological membranes [3]. Around 450 drugs are available in the market which contains carboxylic acid in their structure and it is considered as privileged functional group. Molecular docking studies, on -COOH demonstrated that carboxylate anion can establish strong electrostatic interactions with basic amino acids present in the active site of protein target such as arginine, proline and lysine. This group can act as hydrogen bond donor and acceptor [5-7].

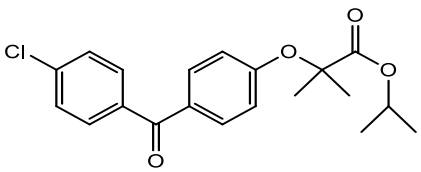


Fig: 1

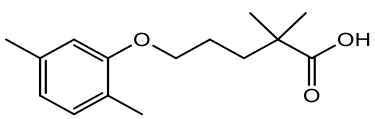


Fig: 2

In view of the therapeutic ability of phenoxy acids and their derivatives, we have selected around 234 compounds from the literature to predict their molecular and pharmacokinetic properties [8-20]. In this work an attempt has been made to study the effect of branching, presence of heterocyclic groups, amidation, esterification, and hydrazone moiety on ADME properties of phenoxy acetic acid. Phenoxy acetic acid structure was used as scaffold structure and effects on ADME properties were studied. Hypothetical molecules were built wherever necessary for better comparison and understanding. Wherever correlation was observed between theoretical and practical values, it was explained with suitable example.

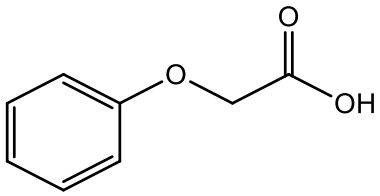
MATERIALS AND METHODS

Prediction of Molecular and Pharmacokinetic descriptors

Molecular descriptors, such as log P (partition coefficient), molecular weight (MW), the acceptors and donors for hydrogen bonding in a molecule and topological polar surface area (TPSA) were calculated using the online software (http://www.molinspiration.com/). The "Lipinski rule" states that orally bioavailable molecules fulfil the following criteria: log p ≤5, molecular weight ≤500, hydrogen bond acceptors ≤10, and hydrogen bond donors ≤5. The percentage of absorption was estimated using the equation: % ABS = 109 − (0.345 × TPSA). Absorption, distribution, metabolism and excretion (ADME) properties of molecules were predicted using the preADMET online server (http://preadmet.bmdrc.org/). This program calculates the *in vitro* Caco-2 cell permeability (<4 - low, (4-70)-moderate, >70-high permeability), skin permeability, plasma protein binding (>90 - strongly bound, <90-weakly bound) and blood brain barrier penetration (BBB) (>1 - CNS active compounds (+),<1 - CNS inactive compounds (-).

RESULTS AND DISCUSSIONS

Molecular properties and ADME descriptors for the scaffold structure phenoxy acid (Fig: 3) were calculated. The predicted molecular and ADME descriptors such as log P, TPSA, % ABS and %PPB are presented in Table.1 which showed that the predicted lipophilicity of phenoxy acid is 1.24, indicating that incorporation of various substituent groups on to the molecule are possible to obtain orally active compound. Phenoxy acetic acid has good percentage absorption (92.94) while BBB >1 (1.22) suggests that this acidic moiety is having considerable CNS permeability. Percentage plasma protein binding of phenoxy acid is very less (39.12) indicating that drug interactions of this compound is very less. Molecular weight of this interesting molecule is 166.18, which explains its suitability as a lead molecule for the insertion of substituent groups.



Phenoxy acetic acid (PA)

Fig: 3

Table 1: Important molecular and ADME parameters of phenoxy acid

Descriptors	PA
Log P	1.24
TPSA	46.53
MV	136.83
% ABS	92.94
PPB	39.117
BBB	1.22

Effect of branching

To study effect of branching on ADME profile phenoxy acid moiety, we build hypothetical molecules and calculated the properties which are given in table 2. From the Table it can be observed that as the TPSA values of these derivatives are similar, there is no effect on absorption of acids when they are extended with one, two groups or when they are branched (3-phenoxypropanoic acid, 2, 2-dimethyl-3-phenoxypropanoic acid, 3-phenoxypentanoic acid, 3-phenoxybutanoic acid) (4a-d).

Table 2: Important molecular and ADME parameters of 4a-4d

Descriptor	Log P	TPSA	MV	%ABS	PPB	BBB
4a	1.51	46.53	153.63	92.94	80.50	1.65
4b	2.40	46.53	186.46	92.94	95.38	2.90
4c	2.38	46.53	187.02	92.94	97.08	1.33
4d	1.87	46.53	170.22	92.94	91.74	1.57

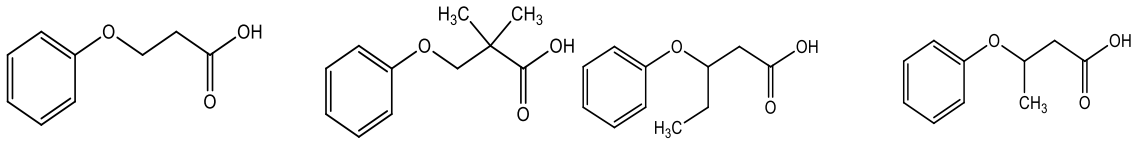


Fig: 4a-4d

Effect of heterocyclic groups

When theoretical properties were predicted, topological surface area (TPSA) is enhanced when the phenyl ring is substituted with thiazole (59.42) (5a), oxazole (72.56) (5b) and pyrazole (71.26) (5c), Oxazole with its nitrogen and oxygen raised TPSA volume to a great extends in comparison to the thiazole substitution. It is also observed that percentage plasma protein binding of unsubstituted phenoxy acid is very less (39.12), whereas when the ring is substituted with thiazole heterocyclic it is enhanced to 85.79 and with the introduction of oxazole and pyrazole it raised from 39.117 to 64.28 and 64.98 respectively. When phenoxy acetic acid is substituted with morpholine, hydrophilicity of the derivative is increased (0.48), percentage absorption is appreciable (85.61) and percentage plasma protein binding is very less (20.15) in comparison to other heterocyclic substituted phenoxy acids. From these results, it can be demonstrated that distribution of this derivative is less and it may have less drug interactions.

We have calculated theoretical properties for 58 molecules available in the literature containing heterocyclic groups on phenoxy acid scaffold which are summarized in table.1 in the supplementary material [8-12]. The results showed that all the compounds meet the lipinski rules of the five with predicted scores of < 5 for lipophilicity, ranging from 1.19 to 4.58. Most of the compounds also showed TPSA value < 150A°, indicating good permeability in the plasma membrane. The percentage of absorption (% ABS) values calculated ranged from 48.72 to 84.34.

Calculation of drug likeness score for these compounds revealed that most of them are moderately active as GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and enzyme inhibitors. Few compounds are highly active as GPCR ligands (1-10: 0.1-0.11), ion channel modulators (2, 3, 6, 9, 10 - 0.03-0.05) nuclear receptor ligands (1-10: 0.26-0.49) and some of them are active as enzyme inhibitors (1-3, 9, 24, 28, 31:0.00-0.07).

Table 3: Substitution of phenoxy acid with heterocyclic rings

Descriptors	Thiazole (5a)	Oxazole (5b)	Pyrazole (5c)	Oxadiazole (5d)	Pyrimidine (6a)	Morpholine (6b)	Indole (7a)	Benzisoxazole (7b)	Piperidine (7c)
Log P	1.84	1.20	1.12	1.11	1.26	0.48	3.23	2.80	1.52
TPSA	59.42	72.56	71.26	85.46	72.32	67.79	62.32	72.56	58.56
MV	194.79	185.65	189.31	181.50	199.93	214.61	23722	229.64	222.43
%ABS	88.50	83.96	84.41	79.51	84.04	85.61	87.49	83.96	88.79
%PPB	85.79	64.28	64.98	62.84	46.34	20.15	86.70	92.39	25.48
BBB	0.107	0.109	0.021	0.125	0.258	0.018	0.554	0.011	0.026

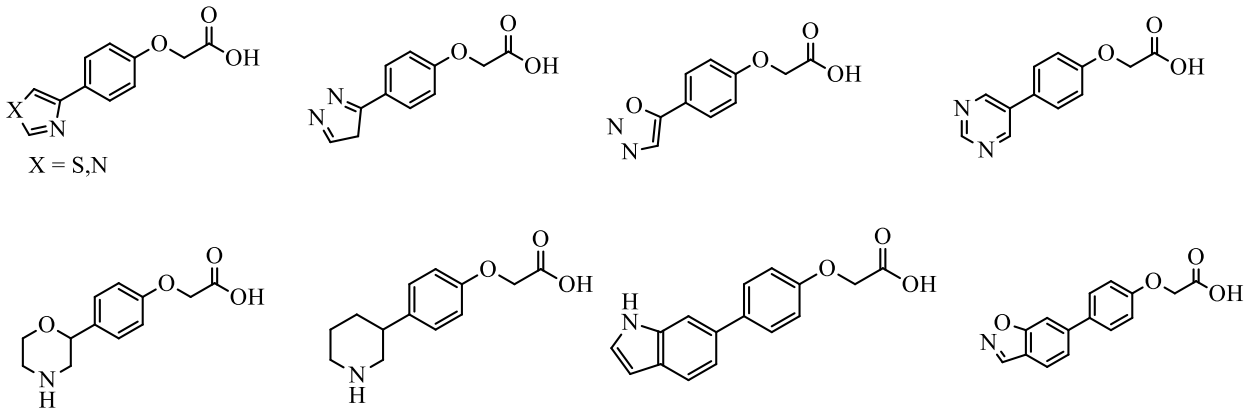


Fig: 5a-d (phenoxy acids bearing five–membered heterocyclic rings)
Fig: 6a-c (phenoxy acids bearing unsaturated and saturated six–membered heterocyclic rings)
Fig: 7a-b (phenoxy acids bearing fused heterocyclic rings)

Influence of esterification on phenoxy acids

Phenoxy butanoic acid and atropine are predicted to have very good CNS permeability, but esterification leads to loss of CNS activity. We have calculated theoretical properties for 1 molecule available in the literature containing ester group on phenoxy acid scaffold is summarized in table.2 and in supplementary material in table.5. The results showed that the compound meet the lipinski rule of the five. The compound also showed TPSA of less than 150A°, indicating a good permeability of the drug in the cellular plasma membrane. The percentage of absorption (% ABS) value is 95.62%.

We have calculated theoretical properties for 2 molecules available in the literature containing phenoxy esters which are summarized in table.2 in the supplementary material [13-14].

Table 4: Substitution of phenoxy acid with ester

Descriptors	PA	Atropine(8)	2-phenoxybutanoic acid(9a)	SM21(9b)
LogP	1.24	2.42	2.11	4.76
TPSA	46.53	58.56	46.53	38.78
MV	136.83	306.03	170.22	326.88
%ABS	92.94	88.7968	92.94715	95.62
% PPB	39.114	35.26	83.68	83.41
BBB	1.22	0.0508	2.024	0.28

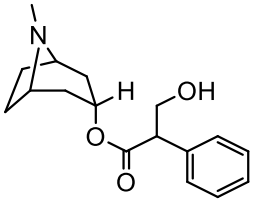
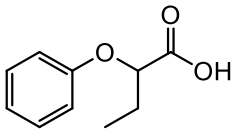


Fig: 8



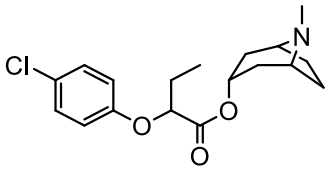


Fig: 9a-b

Calculation of drug likeness score for the compound revealed that the compound is active as GPCR ligand (0.31), ion channel modulator (0.06), nuclear receptor ligand (0.12), protease inhibitor (0.13) enzyme inhibitor (0.08) and moderately active (-0.27) as kinase inhibitor.

Effect of N-acylhydrazone formation on ADME profile of phenoxy acids

Conversion of phenoxy acid to N-acylhydrazone and aryl-N-acylhydrazones increased lipophilicity and % PPB whereas CNS permeability is predicted to be decreased as per the Table.5 Phenyl hydrazide moiety increased lipophilicity and PPB, whereas BBB value is indicating CNS impermeability.

Table: 5 Substitution of phenoxy acid with aceto hydrazides

Descriptors	PA	4-oxo butanoic acid (Fig.10)	4-[4-(carboxymethoxy)phenyl] -4-oxobutanoic acid(Fig.11)	2-phenoxy-*N*'-[(*E*)-phenylmethylidene]aceto hydrazide (Fig.12)
LOGP	1.24	1.25	0.55	3.07
TPSA	46.53	54.37	100.90	50.70
MV	136.83	163.63	216.42	235.88
%ABS	92.94	90.24	74.1895	91.50
%PPB	39.114	87.13	69.48	99.12
BBB	1.22	1.08	0.00826357	0.477

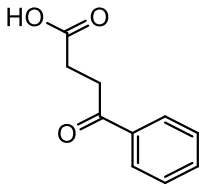


Fig: 10

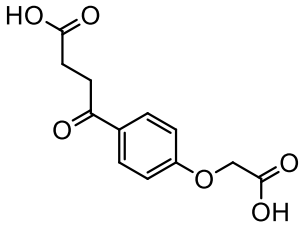


Fig: 11

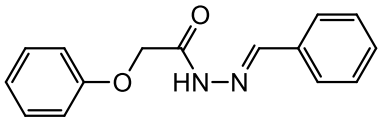


Fig: 12

Predicted values infer that different phenoxy acids such as phenoxy acetic acid, 4-oxo butanoic acid (Fig.10)(1.08), phenoxy propanoic acid, 2, 2-dimethyl-3-phenoxy propanoic acid have very good CNS penetration, hydrazide derivation of phenoxy propionic acid (Fig: 12) drastically decreased CNS permeability (0.47) which is given in Table.5. Pre ADME studies demonstrated that the derivative has good absorption in the intestine and distribution.

Table 6: Substitution of phenoxy acid with aceto hydrazides

Descriptors	2-methyl-2-phenoxy-*N*'-[(*E*)-phenylmethylidene] Propane hydrazide	2-phenoxy-*N*'-[(*E*)-phenylmethylidene]butane hydrazide	2-phenoxy-*N*'-[(*E*)-phenylmethylidene] propane hydrazide
LOGP	3.88	3.42	2.92
TPSA	50.70	50.36	50.36
MV	268.71	258.42	241.61
%ABS	91.50	91.62	91.62
%PPB	94.54	93.35	95.60
BBB	0.63	3.53	2.43

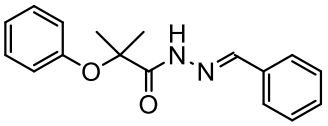
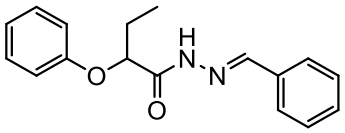


Fig: 13



Figs: 14

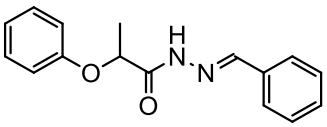


Fig: 15

We have calculated theoretical properties for 16 molecules available in the literature containing phenoxy aceto hydrazides which are summarized in Table.3 in supplementary material [15-16]. The results showed that except few compounds (11, 13 and 14) all the compounds obeyed the lipinski rules of the five and the percentage of absorption (% ABS) values ranged from 81.952 to 91.50, indicating good absorption in the gut.

Calculation of drug likeness score towards these compounds revealed that all of them are moderately active as GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and enzyme inhibitors (-5.0 to 0.0).

Turan–Zitouni *et al* synthesized aryl propionic acid derivatives with N-acylhydrazone moiety and evaluated them for antinociceptive, anti-inflammatory activity using different animal models. The results demonstrated that these derivatives were active in peripherally mediated antinociceptive and anti-inflammatory activities while all of them were inactive in centrally mediated activities. In this study correlation was observed between predicted values and *in vivo* results (BBB >1).

Influence of amidation on ADME properties of phenoxy acetic acid

Table 7: Substitution of Phenoxy acid with amide group

ADME	PA	2-Phenoxy acetamide (fig:16)	2-phenoxy-N-phenylacetamide (fig:17)
LOGP	1.24	0.73	2.80
TPSA	46.53	52.53	38.33
MV	136.83	140.10	212.62
% ABS	92.94	85.45	91.75
% PPB	39.117	10.65	95.56
BBB	1.22	0.57	0.83

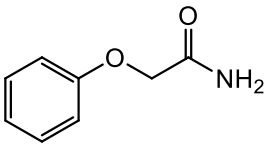


Fig: 16

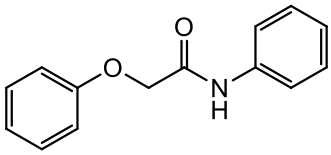


Fig: 17

Important molecular and ADME properties were compared for unsubstituted phenoxy acid, its amide derivative and 2-phenoxy N-phenyl acetamide derivatives using hypothetical molecules. As per the results amidation of phenoxy acid (Fig: 18) decreased the lipophilicity (0.73), percentage absorption (85.45) and percentage protein binding (10.65) whereas amidation using aromatic amine (2-phenoxy N-phenyl acetamide) (Fig: 33) led to compounds with good absorption and distribution properties. One important observation regarding CNS permeability is amidation either with NH_3 or aromatic amines leads to CNS inactive agents (Fig: 32, Fig: 33). With the introduction of electron withdrawing agents CNS permeability is decreased.

There are several phenoxy amides available in the literature which showed pharmacological properties such as antipyretic, hypoglycaemic, anticancer, antinociceptive, anti-inflammatory etc. We have calculated theoretical properties for 109 molecules available in the literature containing phenoxy amides which are summarized in table.4 in the supplementary material [17-20].

The results showed that except for few compounds (17, 18, 23, 25, 33, 35- 41, 48-52, 51, 52, 56-60) all the compounds meet the Lipinski rules of the five. All compounds showed a PSA of less than 150A°, indicating a good permeability of the drug in the cellular plasma membrane. The percentage of absorption values (% ABS) are found to be in the range of 69-94.07% for these molecules.

Calculation of drug likeness score towards compounds revealed that most of them are moderately active as GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and enzyme inhibitors. Few compounds are active as GPCR ligands (34, 39, 42, 44:0.03-0.06), kinase inhibitors (51, 60, 61: 0.02-0.15), nuclear receptor ligands (23-25, 42: 0.02-0.11).

Based upon these theoretical predictions, it can be concluded that phenoxy acid moiety is good pharmacophoric group present in variety of pharmacologically active agents and chemical modifications of this moiety is feasible with respect to ADME profile and oral bioavailability.

REFERENCES

1. Nicolaou, K. C. (2014). Advancing the Drug Discovery and Development Process. *Angew. Chemie International Edition*, *53*, 9128 – 9140.
2. Ganugapati, J., & Swarna, S. (2014). Molecular docking studies of antidiabetic activity of cinnamon compounds. *Asian Journal of Pharmaceutical and Clinical Research*, *7*(2), 31-34.
3. Begum, S., Bharathi, K., Prasad, K. V. S. R. G. (2016). Review Article: Mini review on therapeutic profile of phenoxy acids and thier derivatives. *International Journal of Pharmacy and Pharmaceutical Sciences*, *8*(10), 66-71.
4. Ballatore, C., Huryn, D. M., & Smith, A. B. (2013). Carboxylic acid (bio) isosteres in drug design. *Chem Med Chem*, 8(3), 385-95.
5. Lassalas, P., Gay, B., Lasfargeas, C., & James, M. J. (2016). Structure Property Relationships of Carboxylic Acid *Isosteres Journal of Medicinal Chemistry*, *59*(7), 3183-203.
6. Oliveira, M. E., Cenzi, G., Nunes R. R., & Andrighetti C. R. (2013). Antimalarial activity of 4-metoxychalcones: docking studies as falcipain /plasmepsin inhibitors, ADMET and lipophilic efficiency analysis to identify a putative oral lead candidate. *Molecules*, *18*, 15276-15287.
7. Rajitha, G., Prasad, K.V. S. R. G., Umamaheswari, A., Pradhan, D., & Bharathi, K. (2014) synthesis, biological evaluation, and

molecular docking studies of N-(a-acetamido cinnamoyl) aryl hydrazone derivatives as antiinflammatory and analgesic agents. *Medicinal Chemistry Research, 23,* 5204–5214.

8. Santosh, N. M., Manjusha, C. N., Nikhil, S. S., &Pritam, N. D. (2014). Synthesis and in-vivo hypolipidemic activity of some novel substituted phenyl isoxazol phenoxy acetic acid derivatives. Bioorganic and Medicinal *Chemistry Letters, 24,* 2155–8.
9. Shahar Yar, M., Afroz Bakht, M., Siddiqui, A. A., & Abdullah, M. M. (2009). Synthesis and evaluation of in vitro antiviral activity of novel phenoxy acetic acid derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry, 24*(3), 876–82.
10. Santosh, N. M., Priyanka, T. S., Devanand, B. S. (2010). Synthesis and hypolipidemic activity of novel 2-(4-(2-substituted aminothiazole-4-yl) phenoxy) acetic acid derivatives. *European Journal of Medicinal Chemistry, 45*, 3096-3100.
11. Anna Pratima, G. N., Choudhari, S., & Hemant, D. U. (2012). Design and synthesis and hypoglycemic activity of novel 2-(4-((2, 4-dioxothiazolidin-5-ylodene)methyl)-2-methoxyphenoxy)-N-subtituted acetamide derivatives. *European Journal of Experimental Biology, 2* (4), 1302-4.
12. Anna Pratima, G. N., Dipali, D., & Hemant, D. U. (2012). Facile synthesis and *in vivo* hypoglycemic activity of novel 2, 4-thiazolidinedione derivatives. *European Journal of Experimental Biology, 2* (2), 343-53.
13. Ghelardini, C., Galeotti, N., Gualtieri, F., Scapecchi, S., & Bartolini, A. (1997). 3-α-Tropanyl2-(4-Cl-phenoxy) butyrate (SM 21): A review of the pharmacological profile of a novel enhancer of cholinergic transmission.CNS *Drug Reviews, 3*(4), 346-62.
14. Ghelardini, C., Galeotti, N., Gualtieri, F., Scapecchi, S., & Bartolini, A. (2000). pharmacological characterization of the novel ACh releaser α-Tropanyl 2-(4-bromophenyl) propionate (PG-9).*CNS Drug Reviews, 6*(1), 63–78.
15. Shekarchi, M., Navidpour, L., & Khorami, A. R. (2011). Synthesis of *N*-arylidene-2-(2-Phenoxyphenyl) Aceto hydrazides as Anti-Inflammatory Agents. *Iranian Journal of Pharmaceutical Research*, *10* (2), 369-377.
16. Turan-Zitouni, G., Yurttas, L., & Kaplancıklı, Z. A. (2014). Synthesis and anti-nociceptive, anti-inflammatory activities of new aroyl propionic acid derivatives including N-acylhydrazone motif. *Medicinal Chemistry Research*, 1309-1.
17. Wei Ang, Yan-Ni, L., Tao Yang, Jian-Zhong, Y., Wei-Yi Pi, & Ying-Hong, Y. (2012). Synthesis and biological evaluation of 2-(3-fluoro-4-nitro phenoxy)-N-phenylacetamide derivatives as novel potential affordable antitubercular agents. *Molecules, 17*, 2248-2258.
18. Malleshappa N. N., Harun, M. P., & Sarita K. (2012). A QSAR Analysis of 2-phenoxy-N-substituted Acetamide Analogues as Hypoxia-Inducible Factor-1(HIF-1) Inhibitors: A Rational Approach to Anticancer Drug Design. *Medicinal Chemistry, 8*, 599-614.
19. Kaplancıkli, Z. A., Yurttas, L., Turan-Zitouni, G., Ozdemir, A., Ozic, R., & Ulusoylar-Yıldırım, S. (2012). Synthesis, antimicrobial activity and cytotoxicity of some new carbazole derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry, 27*(6), 868–74.
20. Lee, K., Lee, J. H., Boovanahalli, S. K., Jin, Y., Lee, M., & Jin, X. (2007). (Aryloxyacetylamino) benzoic acid analogues: A new class of Hypoxia-Inducible Factor-1 Inhibitors. *Journal of Medicinal Chemistry, 50*, 1675-84.