International Journal of Life Science and Pharma Research

SYNTHESIS, CHARACTERIZATION AND INSILICO TOXICITY PREDICTION, ANTI-MICROBIAL STUDY OF ORTHO-AMINO SUBSTITUTED BENZAMIDE DERIVATIVES

SK. AMMAJI*[1],G.PAVAN KUMAR[2], K.LIKHITH[2],K. MADHUSREE[2],K. POOJA[2], AND P.VENKATESH[2]

[*] University College of pharmaceutical sciences, ANU, Guntur (Dt), Andhra Pradesh, India.
[1]Assistant professor, Department of pharmaceutical chemistry, NRI College of Pharmacy, Pothavarappadu, Krishna (Dt), Andhra Pradesh, India.
[2]NRI College of Pharmacy, Pothavarappadu, Krishna (Dt), Andhra Pradesh, India

ABSTRACT

Benzamides are most widely used in medicinal chemistry and play a key role in biological action for treatment of various disorders such as anti-microbial, anti-malarial, anti-cancer, anti HIV, anti-viral, anti ameobic, anti-psychotic. The benzamide was used as an intermediate for synthesis of various medicinal compounds, in the present work; synthesization was carried out by using isatoic anhydride treated with various substituted anilines under acidic condition to form different substituted ortho-amino benzamide derivatives. Evaluation of the synthesized compounds were done by using the *Insilico* toxicity prediction methods with the aid of online software's like OSIRIS, OCHEM, Molinspiration. These three softwares gave the drug score value of 3a, 3c, 3f, 3d and they are nearer to standard drug score value of 0.8. Toxicity prediction inferred that except 3e, other derivatives were safe to inhibit enzyme cytochrome P450 a subunit of CYP 1A2. The enzyme located in endoplasmic reticulum metabolizes the polyunsaturated fatty acids, steroidal hormones, vitamins, and also catalyzes hydroxylation reaction like hydroxyl estrogen from estrogen, 17-beta estradiols and has a major role in synthesis of all Trans retinol biosynthesis in liver. Invitro evaluation of Anti-microbial activity done by disc diffusion method, confirmed the compounds3eand3f had significant activity against *Pseudomonas aeruginosa* and the compounds3aand3dshowed significant activity against *Bacillus subtilis*, whereas the compounds 3c showed good activity against the organism *Bacillus pumilus.* Compound 3a showed moderate antifungal activity against *Candida albicans*. Thus in future benzamides can be considered as an effective intermediate for synthesis of different substituted quinoxaline derivatives.

KEYWORDS: ***Benzamides, Antimicrobial study, DMSO, Insilco toxicity prediction, OSIRIS, OCHEM, molinspiration.***

SK. AMMAJI *

Assistant professor, Department of pharmaceutical chemistry, NRI College of Pharmacy, Pothavarappadu, Krishna (Dt), Andhra Pradesh, India.

Received on: 06-09-2019
Revised and Accepted on: 01-11-2019
DOI: http://dx.doi.org/10.22376/ijpbs/lpr.2019.9.4.P103-110

INTRODUCTION

Benzamides are an identical structural unit present in many compounds having biological activities. They are synthesized from different organic sources that are extracted from natural sources[1,2]. For example proteins play an essential role in all biological process such as immune protection, enzyme catalysis, transport or storage (hemoglobin's) and mechanical support (collagen). In amides, all the three atoms O=C=N chain are reactive which make useful moiety in synthesis of organic compounds[5,6,7]. They have a wide range of biological activities like Antimicrobial, Anti-HIV, Anti-psychotic action (especially block D2 receptors), Anti-diabetic (especially treatment of type-2 diabetes), Anti- Alzheimer's, Anti-Depressants, Anti-Oxidant properties. Some substituted benzamides are therapeutically used as neuroleptics and they possess different kinds of pharmacological activities like analgesic, anti-inflammatory, anti-cancer, cardiovascular and other biological activities[10,12,14]. The present work is to synthesize the ortho-amino substituted benzamide derivatives from isatoic anhydride and substituted aniline under acidic conditions, to evaluate anti microbial activity by disc diffusion method and to find out the active lead molecule by using insilico optimization methods

MATERIALS AND METHODS

All the chemicals and reagents were obtained in synthetic grade from different manufacturer. Isatoic anhydride (Kemphasol), 4-amino phenol (Loba chemicals), 2-amino phenol (Loba chemicals) 4-chloro aniline (Avra chemicals) 4-fluoro aniline (Avra chemicals) Aniline (Loba chemicals) Toluidine (Moly chem) reactions were monitored by TLC (silica gel) and melting points were determined by tempo melting point apparatus.The IR and NMR spectra were recorded on Fourier transform IR spectro meter (model Shimadzu 8700) and Bruker bio-spin spectrometer at 400 MHz using DMSO as standard solvent respectively. The synthesized compound completely soluble in DMSO solution.

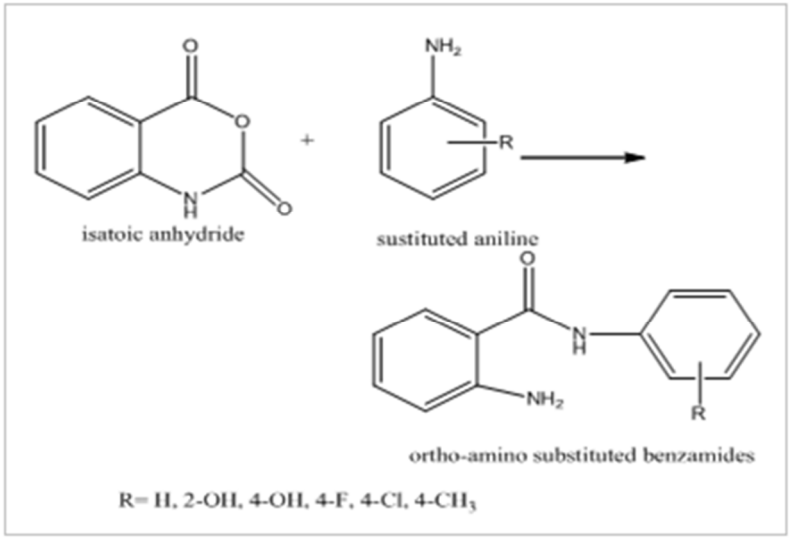

Figure 1
Scheme for *Synthesis of orthoaminobenzamides*

Experimental Procedure

Accurately Weighed equimolar quantities of isatoic anhydride (0.01moles) and different substituted aniline (0.01mole) were taken in a dried round bottomed flask (RBF). 30 ml ethanols were added to dissolve completely the content. Then 2ml concentrated sulphuric acid solution were added in drop wise manner with continuous stirring for 5 minutes. The reflux condenser was fixed and refluxed for 2-3hrs and the reaction is monitored with TLC. After completion of the reaction, the mixture was cooled at room temperature and crushed ice was added. The compound gets precipitated out and the precipitate was filtered; washed with ice cold water for 2 or 3 times and recrystallized with methanol. Data warrior software was used to predict toxicity of the compound. Green colour indicates moderate activity and yellow indicate low activity. OCHEM database toxicity predicted by ames mutagenicity test. From the compound result, inactive indicates non mutagenic towards test organism, active indicates

mutagenic in test organism. It also determines enzyme inhibition of CYP1A2, 2C9, 2C19, 2D6, 3A4. From the results, positive (+) indicates enzyme inhibiting property, negative (-) indicates drug does not inhibit the enzyme activity. Molinspiration database determines bioactivity score and its value less than 0 indicates active compound, greater than -5.0 indicates inactive compound and if ranges between -5.0 to 0.0, indicates moderately active compounds.

STATISTICAL ANALYSIS

For antimicrobial studies, the Student's non-paired *t*-test and ANOVA was used to compare normally distributed values between the groups. $P < 0.01$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Synthesized compounds were recrystallized with methanol to determine its melting point. Percentage yield results shown in table 1 and spectral analysis i.e ^{H}NMR, ^{13}CNMR, MASS, IR studies results shown below.

Spectral analysis of synthesized compounds

ABA: -MASS:-$M+H^+$ = 212, Base peak= 1H-NMR:- Aromatic C-NH (4.722, S, 1H), secondary amide (11.99, S, 1H) IR:- TRS Mode:- C-NH (3746), C=O (1696), C-NH_2 (1553)

4-OHBA: -MASS:-$M+H^+$ = 228, Base peak= 1H-NMR:- Aromatic C-NH (3.38, S, 1H), secondary amide (11.63, S, 1H), OH(8.31, S, 1H)

2-OHBA: - $M+H^+$ = 228, Base peak = 1H-NMR:- Aromatic C-NH (4.226, S, 1H), secondary amide (11.99, S, 1H), OH(8.31, S,1H)

4-FBA: - $M+H^+$ = 230, Base peak= 1H-NMR:- Aromatic C-H (4.722, S, 1H), secondary amide (8.31, S, 1H) IR:- TRS Mode:- C-NH (3742), C=O (1696), Aromatic C-H(2376), C-F (1513)

4-ClBA: - $M+H^+$ = 246, Base peak= 65 1H-NMR:- Aromatic C-H (5.74, S, 1H), secondary amide (8.31, S, 1H) IR:- TRS Mode:- C-NH (3743), C=O (1740), Aromatic C-H(2927), C-Cl(755)

TBA: -$M+H^+$ = 226, Base peak= 1H-NMR:- Aromatic C-H (3.70, S, 1H), secondary amide (11.99, S, 1H), P-Methyl (2.51, S, 1H) IR:- TRS Mode:- C-NH (3742), C=O (1696), Aromatic C-H(2376)

4-AminoBA:-IR:- TRS Mode:- C-NH (3611), C=O (1696), C-NH_2 (1550)

2-AminoBA:-IR:- TRS Mode:- C-NH (3734), C=O (1746)

Table 1
Physico-chemical properties of compounds

S.No	Solubility	Elution ratio (Hexane: ethyl acetate)	R_f value	Reflux hours	Percentage Yield	Melting point
3a(aniline)	DMSO	5:5	0.7	2	70%	180
3b(4-chloro)	DMSO	5:5	0.5	2	67%	195
3c(toluidine)	DMSO	5:5	0.6	3	80%	190
3d(4-flouro)	DMSO	5:5	0.5	3	85%	283
3e(4-amino)	DMSO	5:5	0.4	2	65%	240
3f(2-amino)	DMSO	5:5	0.5	2	75%	245

Insilco and toxicity predictions

The *In silico* and toxicity predictions for the synthesized compounds was carried out by using three online software's

- OSIRIS- www.organic-chemistry.org/prog/peo/tox.html
- OCHEM- https://ochem.eu
- Molinspiration-www.molinspiration.com

Table 2
OSIRIS Calculations

Compound	Toxicity Risks				Molecular Properties Calculation				
	MUT	TUMO	IRRI	REP	M.W	CLP	logS	DL	DS
o-amino-phenyl benzamide(3a)					212	2.4	-4.08	2.68	0.76
o-amino-4-hydroxy phenyl benzamide(3b)					228	2.43	-5.02	2.36	0.65
o-amino-2-hydroxy-pheyl benzamide(3c)					228	2.59	-4.4	2.74	0.72
o-amino-4-fluoro-phenyl benzamide(3d)					230	3.92	-5.85	3.68	0.52
o-amino-4-chloro-phenyl benzamide(3e)					246	3.31	-5.12	3.38	0.5
o-amino-4-methyl-phenyl-benzamide(3f)					226	2.76	-4.91	3.64	0.67
Ciprofloxacin					331	-1.33	-1.83	5.43	0.81
Clotrimazole					344	-0.11	-2.17	1.99	0.87

MUT: Mutagenic; TUMO: Tumorigenic; IRRI: Irritant; REP: Reproductive Effective; CLP: CLogP; Log s: Solubility mol/lit; DL: Drug-Likeness; DS: Drug-Score. MW: Molecular weigh

Green box indicate moderate inhibiting activity, yellow box for low activity.

Table 3
Online Chemical Modeling

Compound	Aqueous solubility	Log IGC50	AMES	CYP3A4	CYP2D6	CYP2CI9	CYP2C9	CYP1A2
o-amino-phenyl benzamide(3a)	2.88	1.22	Active	–	–	–	+	+
o-amino-4-hydroxy phenyl benzamide(3b)	3.93	0.57	Active	–	–	–	+	+
o-amino-2-hydroxy-pheyl benzamide(3c)	3.41	0.78	Active	–	–	+	+	+
o-amino-4-fluoro-phenyl benzamide(3d)	4.53	1.22	Active	–	–	+	–	+
o-amino-4-chloro-phenyl benzamide(3e)	3.86	1	Active	–	–	+	–	+
o-amino-4-methyl-phenyl-benzamide(3f)	4.44	0.55	Active	–	–	+	+	+
Ciprofloxacin	3.11	0.23	Inactive	–	–	–	–	–
clotrimazole	1.8	0.15	inactive	–	–	–	–	–

+ Inhibitor, - Non inhibitor, AQ-aqueous, IGC 50-Environmental toxicity

Table 4
Molinspiration drug likeness properties

Name of the compound	Log P	Polar Surface Area	H-Bond Acceptors	H-Bond Donor	Volume
o-amino-phenyl benzamide(3a)	2.26	55.12	2	3	198.13
o-amino-4-hydroxy phenyl benzamide(3b)	1.78	75.35	3	2	206.14
o-amino-2-hydroxy-pheyl benzamide(3c)	2.0	75.35	4	2	206.14
o-amino-4-fluoro-phenyl benzamide(3d)	2.43	55.12	2	3	203.06
o-amino-4-chloro-phenyl benzamide(3e)					

	2.94	55.12	4	3	211.6
o-amino-4-methyl-phenyl-benzamide(3f)	2.71	55.12	2	3	214.12

Table 5
Bioactive score results of synthesized compounds

Name of the compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor
o-amino-phenyl benzamide(3a)	-0.42	-0.18	-0.22	-0.82	-0.42
o-amino-4-hydroxy phenyl benzamide(3b)	-0.28	-0.09	-0.08	-0.50	-0.31
o-amino-2-hydroxy-pheyl benzamide(3c)	-0.33	-0.33	-0.14	-0.62	-0.44
o-amino-4-fluoro-phenyl benzamide(3d)	-0.33	-0.17	-0.10	-0.67	-0.37
o-amino-4-chloro-phenyl benzamide(3e)	-0.34	-0.16	-0.17	-0.74	-0.40
o-amino-4-methyl-phenyl-benzamide(3f)	-0.40	-0.26	-0.20	-0.75	-0.42
ciprofloxacin	-0.15	-0.24	-0.53	-0.09	-0.04
clotrimazole	0.04	0.01	-0.09	-0.23	-0.09

The derivatives of synthesized compounds were evaluated by three online soft ware's-OSIRIS, MOLINSPIRTION, OCHEM, from the above table , table no 2,3,4,5 results predicted that the compounds drug score value of 3a, 3c, 3f, 3d were nearer to standard drug 0.8 and other had less value i.e. 0.5. Toxicity prediction inferred that 3e have mutagenic effect than other derivatives and are safe. From OCHEM results all the synthesized compounds found to inhibit subtype CYP 1A2 of CTY P450. MOLINSPIRATION result inferred that all compounds satisfy Lipinski rule 5 and so derivatives found to have kinase and enzyme inhibition properties.

Antibacterial activity

The synthesized compounds (3a-3f) were screened for antibacterial activity studies at a concentration of 50 µg/ml and 100 µg/ml using DMSO as a control against *Bacillus subtilis, Bacillus pumilus, Escherichia coli and Pseudomonas aeruginosa*by disc diffusion method on nutrient agar media. Ciprofloxacin was used as standard drug for the comparison at the concentrations of 50 µg/ml and 100 µg/ml against Gram positive and Gram negative organism. From the data in the Table No-6,**"+"** indicates that the compounds were found to possess moderate and weak activity although several ortho-amino benzamide were reported for antibacterial activity but some of synthesized compounds failed to produce significant antibacterial activity. The compounds 3e and 3f showed a significant activity against *Pseudomonas aeruginosa* and the compound3a and3d showed significant activity against *Bacillus subtilis*, whereas the compound 3c showed good activity against the organism *Bacillus pumilus* rest of the compounds shown weak activity when compared to the standard Ciprofloxacin.

Antifungal activity

From the antifungal data in the Table No 7, it is clear that the synthesized ortho-amino benzamide derivatives possess weak antifungal activity, only the compound 3a shown moderate antifungal activity against *Candida albicans*, whereas the rest of the compounds fail to show significant antifungal activity.

Table 6
Antibacterial activity of synthesized compounds (3a-3f)

Sample Code	*Inhibition zone diameter in mm							
	B.subtilis		*B.pumilus*		*E.coli*		*P. aeruginosa*	
	50 μg	100μg	50μg	100μg	50μg	100μg	50μg	100μg
3a	7.1±0.23	16.1±0.3	4.2±0.23	8.1±0.1	6.1±0.1	8.1±0.2	7.1±0.1	11.1±0.2
3b	5.1±0.1	12.6±0.1	7.2±0.1	14.2±0.2	6.2±0.3	9.2±0.1	7.1±0.1	11.2±0.1
3c	6.0±0.1	13.3±0.2	9.1±0.3	18.1±0.2	5.5±0.1	8.1±0.2	5.2±0.2	10.2±0.1
3d	4.1±0.2	26.0±0.1	4.2±0.2	9.1±0.12	7.5±0.2	13.2±0.2	5.2±0.2	12.3±0.2
3e	7.1±0.24	8.1±0.2	6.5±0.2	14.2±0.1	5.2±0.2	8.5±0.1	4.2±0.1	18.2±0.3
3f	4.2±0.5	9.1±0.2	6.5±0.2	11.1±0.2	4.1±0.1	9.2±0.1	7.1±0.1	19.3±0.3
Ciproflo xacin	20.0±0.2	32.0±0.1	20.0±0.2	33.0±0.2	21.1±0.1	30.1±0.2	22.1±0.1	31.2±0.1
DMSO	-	-		-	-	-	-	-

Note: '-' denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 above good activity. P < 0.01, n =3

Table 7
Antifungal activity of synthesized compounds (3a-3f)

Sample Code	Inhibition zone diameter in mm	
	A.niger	C.Albicans
	100 μg/ml	100 μg/ml
3 a	7.2±0.23	**15.5±0.3**
3 b	6.2±0.1	10.1±0.2
3 c	8.3±0.1	11.1±0.2
3 d	6.2±0.2	9.2±0.2
3 e	4.2±0.2	8.2±0.1
3 f	6.2±0.2	10.2±0.2
Clotrimazole	24.1±.1	26.1±0.1
DMSO	**-**	**-**

Note: 06 – 08 mm poor activity, 08 – 12 mm moderate activity, 12-15 mm good activity. P < 0.01, n=3

DISCUSSION

The Insilco toxicity prediction compounds possess good drug score value as compared to that of standard drug value and also found good inhibition property towards CYP1A2 sub type of CYP 450 enzyme. From Anti-bacterial screening 3b and 3e showed moderate to weak activity. 3a and 3d compounds were found to possess good activity against *B.Subtilis, B.Pumilus* organisms used for the study and rest of the compounds were found to exhibit weak activity when compared to standard Ciprofloxacin. In antifungal activity screening, when compared to standard Clotrimazole, the synthesized compounds showed minimum antifungal activity against *Candida albicans*.

CONCLUSION

In conclusion, by using ortho substitued benzamides taken as intermediate nucleus for synthesizing different substituted quinoxaline derivatives and can be considered as a potential antimicrobial agents. Thus invitro toxicity prediction paves a good way to elucidate the antimicrobial study for lead compounds.

AUTHORS CONTRIBUTION STATEMENT

Sk.Ammaji conceived present idea for developing a scheme on these derivatives. G. Pavankumar and SK.Ammaji carry out the synthesis and spectral analysis of the compounds. SK. Ammaji and

K.Likith, P.Venkatesh predicted the Insilco toxicity by using database tools. K.Madhusree and K.Pooja carried out the biological evaluation of the synthesized compounds. The results were analysed and manuscript were drafted by SK.Ammaji, G.Pavankumar, K.Likhith, K.Madhusree, K.Pooja.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Park K, Lee BM, Hyun KH, Han T, Lee DH, Choi HH. Design and Synthesis of Acetylenyl Benzamide Derivatives as Novel Glucokinase Activators for the Treatment of T2DM. ACS Med Chem Lett. 2015;6(3):296–301. DOI: 10.1021/ml5004712
2. Diness F, Bjerrum NJ, Begtrup M. Synthesis and stability of strongly acidic benzamide derivatives. Beilstein J Org Chem. 2018;14:523–30. DOI: 10.3762/bjoc.14.38
3. Dini K. Synthesis of N-(phenylcarbamothioyl)-benzamide derivatives and their cytotoxic activity against MCF-7 cells. J Chinese Pharm Sci. 2018;27:696–702. DOI: 10.5246/jcps.2018.10.071
4. Magar RL, Thorat PB, Waware JL, More RR, Solanke UA, Patil BR. Synthesis of Some Novel 3-Substituted Indole Derivatives Using Polyamine Functionalized Heterogeneous Catalyst. J Heterocycl Chem. 2014;52(6):1684–92. DOI: 10.1002/jhet.2265
5. Xu J, Lecanu L, Tan M, Greeson J, Papadopoulos V. Identification of a Benzamide Derivative that Inhibits Stress-Induced Adrenal Corticosteroid Synthesis. Molecules. 2009;14(9):3392–410. DOI: 10.3390/molecules14093392
6. Meshesha Tulu M, Yimer AM. Catalytic Studies on Schiff Base Complexes of Co(II) and Ni(II) Using Benzoylation of Phenol. Mod Chem Appl. 2018;06(02). DOI: 10.4172/2329-6798.1000260
7. Ding, H.; Chen, K.; Song, B.; Deng, C.; Li, W.; Niu, L.; Bai, M.; Song, H.; Zhang L. Synthesis and Smo Activity of Some Novel Benzamide Derivatives. Molecules. 2017;23(1):85. DOI: 10.3390/molecules23010085
8. Novanna M, Kannadasan S, Shanmugam P. Phosphotungstic acid mediated, microwave assisted solvent-free green synthesis of highly functionalized 2ˈ-spiro and 2, 3-dihydro quinazolinone and 2-methylamino benzamide derivatives from aryl and heteroaryl 2-amino amides. Tetrahedron Lett. 2019;60(2):201–6. DOI: 10.1016/j.tetlet.2018.12.011
9. Pannala P, Reddy PN, Subba Reddy B V, Misra S, Dhevendar K, Jadav SS. Synthesis, Molecular Docking, in vitro Antiproliferative and Antioxidant Activity of Novel Pyrrolidinyl-Carbazole Derivatives. Curr Org Synth. 2018;14(8). DOI: 10.2174/1570179414666170606120934
10. Settypalli T, Chunduri VR, Maddineni AK, Begari N, Allagadda R, Kotha P. Design, synthesis, in silico docking studies and biological evaluation of novel quinoxaline-hydrazide hydrazone-1,2,3-triazole hybrids as α-glucosidase inhibitors and antioxidants. New J Chem. 2019;43(38):15435–52. DOI: 10.1039/c9nj02580d
11. Zhu P, Fu H, Fang H. Design, Synthesis and Antiproliferative Activities Evaluation of Thiazolopyrimidines Derivatives through Biginelli Reaction. Lett Drug Des Discov. 2017;14(12). DOI: 10.2174/1570180814666170512123132
12. Grewal AS, Kharb R, Prasad DN, Dua JS, Lather V. Design, synthesis and evaluation of novel 3,5-disubstituted benzamide derivatives as allosteric glucokinase activators. BMC Chem. 2019;13(1). DOI: 10.1186/s13065-019-0532-8
13. Chiou W-H, Ojima I. New Cyclization and Cycloaddition Reactions in Organic Synthesis. NATO Science Series II: Mathematics, Physics and Chemistry. Springer Netherlands; 2008. p. 55–83. DOI: 10.1007/978-1-4020-6793-8_3
14. Shuowu. Articles of Significant Interest Selected from This Issue by the Editors. J Virol. 2017;91(18). DOI: 10.1128/jvi.01223-17
15. Iglesias AL, Miranda-Soto V, Pompa-Monroy DA, Martinez-Ortiz JG, Diaz-Trujillo GC, Villarreal-Gomez l. J. Biological Activity of New Schiff Base Compounds Derived from Substituted 3-Aminopyrazoles, the Role of Pyrazole on Bioactivity. Indian J Pharm Sci. 2019;81(2). DOI; 10.36468/pharmaceutical-sciences.515
16. Chen M, Jin H, Tao K, Hou T. Synthesis and

bioactivity evaluation of novel benzamide derivatives containing a diphenyl ether moiety. J Pestic Sci. 2014;39(4):187–92. DOI: 10.1584/jpestics.d14-037

17. Zaheer Z, Shaikh SI, Mokale SN, Lokwani DK. Synthesis, Biological Evaluation and Computational Study of New Quinoline Hybrids as Antitubercular Agent. Lett Drug Des Discov. 2018;15(9):914–22. DOI: 10.2174/1570180814666171026155930
18. Nian S, Yu Z, Tan X, Gan X, Huang M, Zhou Y, et al. Synthesis and Biological Evaluation of N-(5-(2,5-dimethyl-phenoxy)-2,2-dimethylpentyl)-benzamide Derivatives as Novel Farnesoid X Receptor (FXR) Antagonist. Lett Drug Des Discov. 2018;15(9):923–36. DOI: 10.2174/1570180815666171226150403
19. Mabkhot Y, Al-Majid A, Barakat A, Al-Showiman S, Al-Har M, Radi S. Synthesis and Biological Evaluation of 2-Aminobenzamide Derivatives as Antimicrobial Agents: Opening/Closing Pharmacophore Site. Int J Mol Sci. 2014;15(3):5115–27. DOI: 10.3390/ijms15035115
20. Koppireddi S, Chilaka DRK, Avula S, Komsani JR, Kotamraju S, Yadla R. Synthesis and anticancer evaluation of 3-aryl-6-phenylimidazo[2,1-b]thiazoles. Bioorg Med Chem Lett. 2014;24(23):5428–31. DOI: 10.1016/j.bmcl.2014.10.030
21. Ramanathan A, Subramaniam B. Metal-Incorporated Mesoporous Silicates: Tunable Catalytic Properties and Applications. Molecules. 2018;23(2):263. DOI: 10.3390/molecules23020263
22. Pinninti SK, Parimi U. Synthesis And Biological Evaluation Of Amide Derivatives Of Thiazoles As Anticancer Agents. Int Res J Pharm. 2018;9(10):89–93. DOI: 10.7897/2230-8407.0910232
23. Wanjari. Synthesis, characterization and biological evaluation of computational study for prediction of some novel N-1, 3benzothiazole-2-carbonothioyl 2/4substituted benzamides. Inter JChemTech Res. 2017;10(7):401–8.
24. Trotsko N, Przekora A, Zalewska J, Ginalska G, Paneth A, Wujec M. Synthesis and in vitro antiproliferative and antibacterial activity of new thiazolidine-2,4-dione derivatives. J Enzyme Inhib Med Chem. 2017;33(1):17–24. DOI: 10.1080/14756366.2017.1387543
25. Mirza B. An efficient metal-free synthesis of 2-amino-substituted-4(3 H)-quinazolinones. Tetrahedron Lett. 2016;57(1):146–7. DOI: 10.1016/j.tetlet.2015.11.085