Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Research article

Lemon juice catalysed efficient one-pot synthesis and *in silico* ADME prediction of 2-(substituted phenyl) phthalazin-1(2*H*)-ones

Firoz A. Kalam Khan[1*], Amjad Ali[2], Sayyed Mateen[3]

[1]*School of Pharmacy, Anjuman-I-Islam's Kalsekar Technical Campus, Navi Mumbai 410206 (MS), India.*
[2]*Department of Pharmaceutical Chemistry and Quality Assurance, Oriental College of Pharmacy, Navi Mumbai 400 705, (MS) India.*
[3]*Department of Pharmacology, Oriental College of Pharmacy, Navi Mumbai 400 705, (MS) India.*

Received on: 05/03/2021, Revised on: 29/04/2021, Accepted on: 15/05/2021, Published on: 01/07/2021.

***Corresponding Author :** Firoz A. Kalam Khan, School of Pharmacy, Anjuman-I-Islam's Kalsekar Technical Campus, Navi Mumbai 410206 (MS), India.
Email id: firozakhan05@gmail.com

Keywords: Lemon juice, Phthalazin-1(2*H*)-ones; Phthalaldehydic acid; Substituted phenyl hydrazine; One-pot synthesis; ADME.

Vol. 8 (3): 42-48, Jul-Sep, 2021.

Abstract

Recently, lemon juice has received a lot of attention as a highly efficient and selective biocatalyst for organic synthesis. Lemon juice has a lot of potential as a green chemistry catalyst because it is readily available, affordable, biodegradable, and nontoxic. A simple one-pot, synthetic method for the preparation of 2-(substituted phenyl) phthalazin-1(2*H*)-ones **3(a-j)** is described through the reaction of phthalaldehydic acid, substituted phenyl hydrazine and lemon juice as catalyst. The major advantages of the proposed method are its simplicity, short reaction time, easy work-up, inexpensive catalyst, and good yields. ADME properties were predicted in silico and support the potential of **3(a-j)** to show favorable drug-like properties.

Introduction

Green chemistry involves simple and environmentally friendly synthetic aspects with chemical processes and products through the invention of novel reactions that can intensify the desired products and decrease the by-products, as well as a new synthetic procedure that can streamline operations in chemical production [1, 2]. Greener approaches in organic synthesis always help overcome the use and generation of toxic and hazardous substances which involve the use of non-toxic, and inexpensive biocatalysts. These reactions have been extensively investigated in organic synthesis primarily due to their ability to generate complex molecules from simple starting materials using a one-step reaction [3, 4].

A class of condensed heterocycles known as phalazinones exhibits significant biological activity. Phthalazinones are used to treat a wide range of illnesses, including diabetes [5, 6], asthma [7, 8], hepatitis B [9], hepatitis B [10], vascular hypertension [11], and arrhythmia [12]. Phthalazinones also function as effective antimicrobial agents and poly(ADP-ribose)polymerase-1 inhibitors, and they are useful intermediates in the synthesis of VEGF inhibitors [13]. Azelastine, a phthalazinone derivative, is a well-known antiallergic and antihistaminic medication.

The synthesis of phthalazinones can be accomplished in a number of ways, including cycloaddition [14–18], reduction [19–20], cyclocondensation [21] and biotechnological methods [22]. These methods, however, frequently entail potent acids and bases, harsh reaction environments, and prolonged reaction times, among other things. The creation of new processes for the synthesis of phthalazinones is preferred due to the shortcomings of the reported methods. In keeping with our ongoing interest in the creation of procedures for the synthesis of biologically significant heterocyclic compounds [23-24], we present a fresh

technique for the production of phthalazinones from phthalaldehydic acid and substituted phenyl hydrazines using lemon juice as a catalyst with good yield.

Material and methods

Commercially available phthalaldehydic acid and substituted phenyl hydrazines were used without further purification. A fresh lemon was taken, thoroughly washed with water, cut with a knife, and then pieces were pressed manually. To get clear lemon juice, which was used as a catalyst, the juice was filtered through muslin cloth to remove solid material. The melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G coated (Merck) aluminium plates and visualized by iodine vapour. 1H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer, and the chemical shifts were reported in parts per million (ppm) using tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained with Micromass-QUATTRO-II of WATER mass spectrometer.

General procedure for preparation of 2-(substituted phenyl) phthalazin-1(2H)-ones 3(a-l)

A catalytic amount (3 mL) of lemon juice was added to a mixture of phthalaldehydic acid **1** (10 mmol), substituted phenyl hydrazine **2** (10 mmol), and ethanol (20 ml). The reaction mixture was stirred (250 rpm) at room temperature for 50–70 min. After completion (monitored by TLC), the reaction mixture was poured in water and stirred to get the crude solid material. The obtained crude solid product was filtered and recrystallized using ethanol to get a pure product. All of the compounds from the series **3(a–l)** were prepared using a similar procedure.

Spectral data for some 2-(substituted phenyl) phthalazin-1(2H)-one derivatives

*2-Phenylphthalazin-1(2H)-one (**3a**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.60–8.47 (m, 1H, Aromatic), 8.30 (s, 1H, Aromatic), 7.40–7.12 (m, 8H, Aromatic); MS m/z: 223.30 $[M+H]^+$.

*2-(4-Methoxyphenyl)phthalazin-1(2H)-one (**3c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.40–8.22 (m, 1H, Aromatic), 8.10 (s, 1H, Aromatic), 7.75–7.20 (m, 5H, Aromatic), 7.08–6.90 (m, 2H, Aromatic), 3.65 (s, 3H, OCH_3); MS m/z: 253.35 $[M+H]^+$.

*2-(2-Nitrophenyl)phthalazin-1(2H)-one (**3i**)*

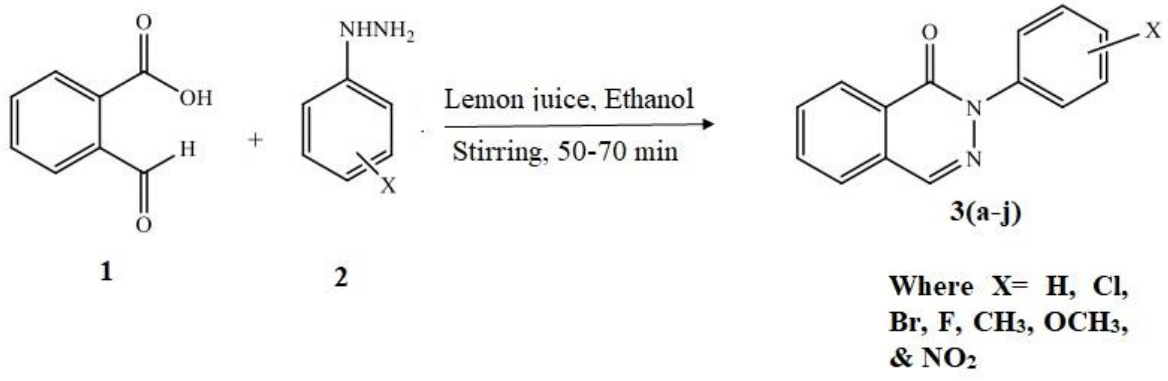
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.48–8.27 (m, 1H, Aromatic), 8.10 (s, 1H, Aromatic), 7.90–7.30 (m, 7H, Aromatic); MS m/z: 268.33 $[M+H]^+$.

ADME properties

A computational study of synthesised compounds **3(a-j)** was carried out in order to predict ADME properties. In this study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog P), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five [25] using Molinspiration online property calculation toolkit [26]. The absorption (% ABS) was calculated by: % ABS= 109- (0.345×TPSA) [27].

Results and discussion

In this study, we report our investigation into an environmentally friendly and highly efficient procedure for the synthesis of 2-(substituted phenyl) phthalazin1(2*H*)-ones **3(a-j)**. Using lemon juice as a catalyst, the compounds were synthesized in good yields from phthalaldehydic acid and various substituted phenyl hydrazines using lemon juice as a catalyst (**Scheme 1**). To the best of our knowledge, there is no literature report of the synthesis of phthalazinones using lemon juice as the catalyst. In addition to effectively catalysing various organic transformations and syntheses, lemon juice is economical, readily available, mild, and easy to handle.



Scheme 1. Synthesis of 2-(substituted phenyl) phthalazin-1(2*H*)-ones 3(a-j).

The effect of catalyst loading on the product yield was investigated (**Table 1**). Using lemon juice in various loads, including 20 mL, 10 mL, 5 mL, 3 mL, and 2 mL, we carried out the reaction for compound (**3a**). The results showed that using 3 mL lemon juice is the most effective, yielding up to 96% of the product.

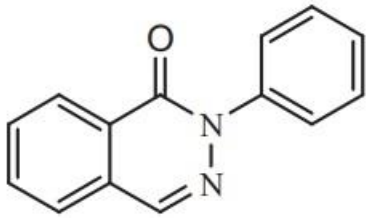
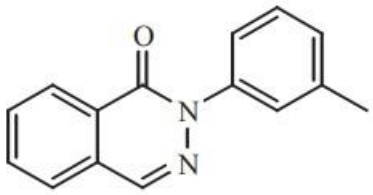
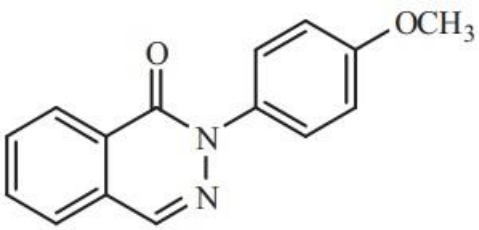
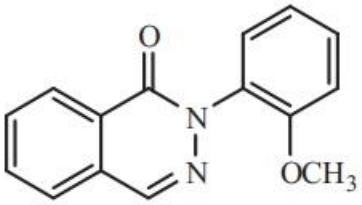
Table 1. Effect of catalyst loading on the yield of 2-phenylphthalazin-1(2*H*)-one (3a).

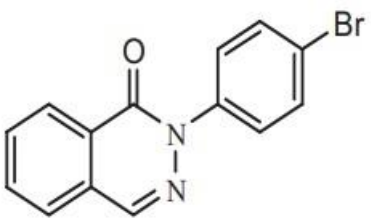
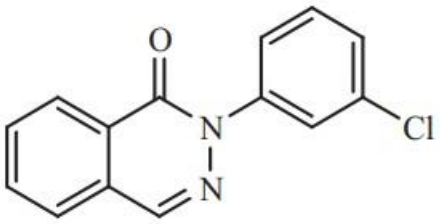
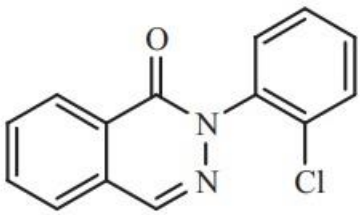
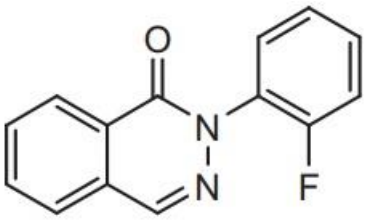
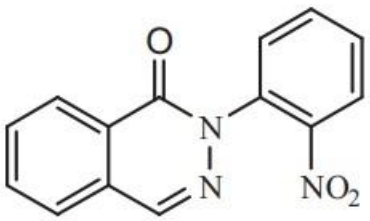
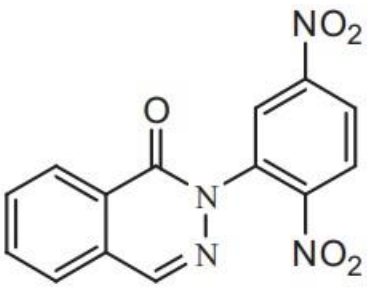
Sr. No.	Catalyst	Quantity (mL)	Yield (%)
1	Lemon juice	20	96
2	Lemon juice	10	96
3	Lemon juice	5	96
4	Lemon juice	3	96
5	Lemon juice	2	85

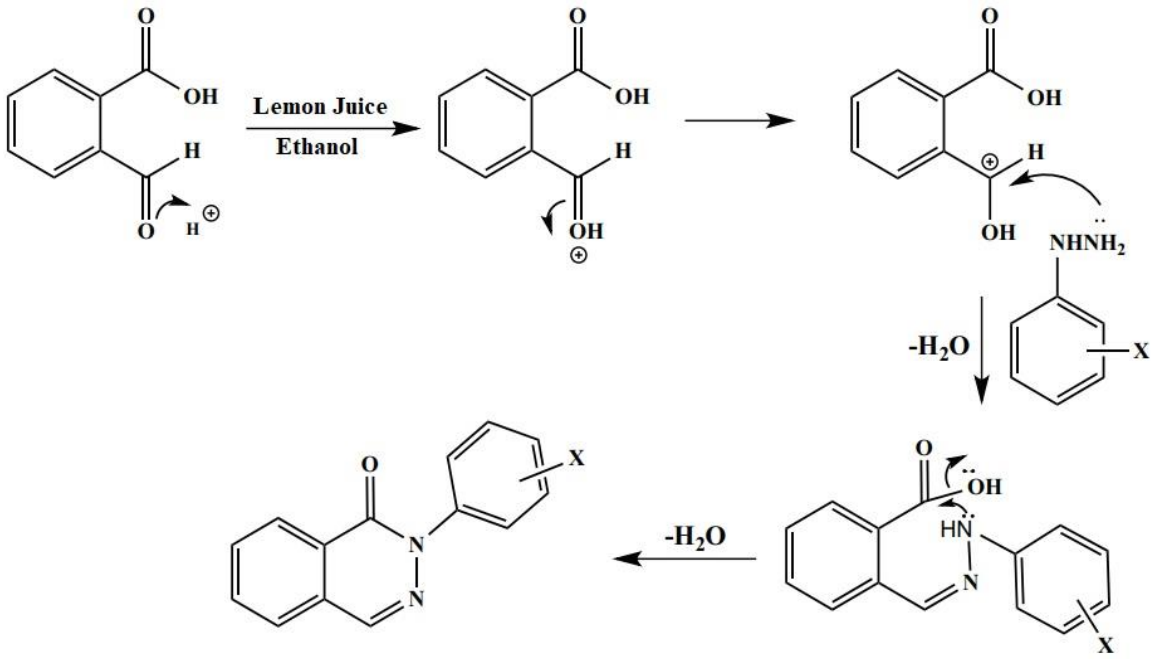
We extended the study under optimal conditions to investigate the suitability of the lemon juice as catalyst for the synthesis of 2-(substituted phenyl) phthalazine-1(2*H*)-ones **3(a-j)**. Under mild conditions, the reaction went smoothly and accommodated a wide range of phenyl hydrazines with an electron-donating and an electron-withdrawing substituent. It should be noted that the products **3(a-j)** were obtained simply by filtering from the reaction medium. The compounds were obtained in high yields (90-97%). TLC was used to monitor the reactions, and the time required for completion was 50-70 minutes. The physical data of the synthesised compounds are presented in **Table 2**.

Using lemon juice as a catalyst, we proposed a possible mechanism for the synthesis of substituted phthalazinones from phthalaldehydic acid and phenyl hydrazine. The target molecules are formed by dehydrative cyclization (**Scheme 2**). Lemon juice's role is to provide the proton required to generate a positive centre at the carbonyl carbon of phthalaldehydic acid. In the first step, there is attack of H^+ on the oxygen of the carbonyl group of phthalaldehydic acid. The formed intermediate rearranges to give a carbocation bearing a positive centre at the carbon of the carbonyl group. In the second step, the lone pair of electrons of NH_2 of phenyl hydrazine is transferred to the active carbocation centre, forming a -C=N bond with the removal of H_2O. The latter is then cyclized to yield the expected phthalazinones by removal of an additional H_2O molecule.

Table 2. Physical data of 2-(substituted phenyl) phthalazin-1(2*H*)-ones 3(a–j).

Entry	Compounds	Time (min)	Yield (%)	Melting point (°C)	
				Observed	Reported
3a		60	96	100-102	104-105 [28]
3b		55	94	46-48	48-50 [29]
3c		50	94	104-106	106-108 [29]
3d		60	97	94-96	98-100 [29]

3e		65	93	164-166	168-170 [30]
3f		60	92	132-136	134-136 [31]
3g		70	90	126-128	124-126 [32]
3h		65	92	124-126	120-122 [28]
3i		65	91	204-206	204-206 [33]
3j		70	90	174-176	176-178 [34]



Scheme 2. Proposed mechanism for the synthesis of 2-(substituted phenyl) phthalazin-1(2*H*)-one 3(a-j).

Table 3. Pharmacokinetic parameters important for good oral bioavailability of 2-(substituted phenyl) phthalazin-1(2*H*)-one 3(a-j).

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON acceptors	n-OHNH donors	Lipinski's violations
Rule					<500	≤5	<10	<5	≤1
3a	96.95	34.90	1	199.64	222.25	2.52	3	0	0
3b	96.95	34.90	1	216.20	236.27	3.16	3	0	0
3c	93.77	44.13	2	225.18	252.27	2.58	4	0	0
3d	93.77	44.13	2	225.18	252.27	2.74	4	0	0
3e	96.95	34.90	1	217.52	301.14	3.33	3	0	0
3f	96.95	34.90	1	213.17	256.69	3.39	3	0	0
3g	96.95	34.90	1	213.17	256.69	3.37	3	0	0
3h	96.95	34.90	1	204.57	240.24	2.85	3	0	0
3i	81.14	80.73	2	222.97	267.24	2.65	6	0	0
3j	65.34	126.55	3	246.31	312.24	2.79	9	0	0

% ABS: percentage absorption; TPSA: topological polar surface area; n-ROTB: number of rotatable bonds; MV: molecular volume; MW: molecular weight; miLog P: logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors: number of hydrogen bond acceptors; n-OHNH donors: number of hydrogen bonds donors.

A computational study of synthesized compounds **3(a-j)** was performed for prediction of ADME properties. The value obtained is depicted in **Table 3**. It is observed that all the synthesized compounds exhibited a good % ABS ranging from 65.34 to 96.95%. Furthermore, none of the synthesized compounds violated Lipinski's parameters. A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: miLog P (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5 [35]. All the active synthesized compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as biologically active oral agents.

Conclusions

In conclusion, using lemon juice as the catalyst, we have developed a very effective process for the synthesis of 2-(substituted phenyl) phthalazin-1(2*H*)-one derivatives from phthalaldehydic acid and phenyl hydrazine. This method has the benefits of simplicity, short reaction times, easy work up, inexpensive catalyst and better yield (90–97%). The present study focused on the importance of fruit juice in organic synthesis with natural and biocatalyst exclusivity. Lemon juice is easily available as a natural and inexpensive catalyst, which makes this protocol green and clean. Analysis of the ADME parameters of synthesized compounds suggested that they have good drug-like properties with potential for oral delivery.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

References

1. Li C.J., Trost B.M. Green chemistry for chemical synthesis. The Proceedings of the National Academy of Sciences, 2008:105(36): 13197-13202.
2. Anjani S., Sheetal S., Gulati S. Green and environmentally benign organic synthesis by using fruit juice as biocatalyst: a review. International Research Journal of Pure & Applied Chemistry, 2018: 16(1):1-15.
3. Simon M.O., Li C.J. Green chemistry oriented organic synthesis in water. Chemical Society Review, 2012:41(4):1415-1427.
4. Anastas P., Eghbali N. Green chemistry: principles and practice. Chemical Society Review, 2010:39(1):301-312.
5. Mylari B.L., Larson E.R., Beyer T.A., Zembrowski W.J., Aldinger C.E., Dee M.F. Novel potent aldose reductase inhibitors: 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2 benzothiazolyl] methyl]-1- phthalazine-acetic acid (zopolrestat) and congeners. Journal of Medicinal Chemistry, 1990:34:108–122.
6. Madhavan G.R., Chakrabarti R., Kumar S.K.B., Misra P., Mamidi R.N.V.S., Balraju V. Novel phthalazinone and benzoxazinone containing thiazolidinediones as antidiabetic and hypolipidemic agents. European Journal of Medicinal Chemistry, 2001:36(7):627–637.
7. Nakajima M., Ohyama K., Nakamura S., Shimada N., Yamazaki H., Yokoi T. Inhibitory effects of azelastine and its metabolites on drug oxidation catalyzed by human cytochrome P-450 enzymes. Drug Metabolism and Disposition, 1999:27(7): 792–797.
8. Ukita T., Sugahara M., Terakawa Y., Kuroda T., Wada K., Nakata A. Novel potent, and selective phosphodiesterase-4 inhibitors as antiasthmatic agents: synthesis and biological activities of a series of 1-pyridylnaphthalene derivatives. Journal of Medicinal Chemistry, 1999: 42(6):1088–1099.
9. El Ashry E.S., Abdel-Rahman A.A.H., Rashed N., Rasheed H.A. Homoacyclovir analogues of unnatural bases and their activity against hepatitis B virus. Pharmazie, 1999:54(12):893–897.
10. Garcia-Cadenas A.E., Olmo E., Lopez J.L., Ferro A., Authi K., Feliciano A.S. Vasorelaxant activity of a new phthalazinones synthesis and studies on the mechanism of action, in: Book of Abstracts, Joint Meeting on Medicinal Chemistry, Aust. Chem. Soc. and Aust. Pharm. Soc., Vienna, Austria 2005:138.
11. Demirayak S., Karaburun A.C., Beis R. Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. European Journal of Medicinal Chemistry, 2004:39(12):1089–1095.
12. Engel J., Kutscher B., Fleischhauer I., Szelenyi S., Metzenauer P., Werner U. New Therapeutic Uses of Phthalazinones Derivatives. European Patent Office, EP0590551 B1 (1994).
13. Cockcroft X., Dillon K., Dixon L., Drzewiecki J., Kerrigan F., Loh V. Phthalazinones 2: Optimisation and Synthesis of Novel Potent Inhibitors of Poly(ADP-Ribose)Polymerase. Bioorganic & Medicinal Chemistry Letters, 2006:16(4):1040–1044.
14. Biniecki S., Moll M. PL Patent 60625. Chemical Abstract, 1970:74:76435.
15. Raoul P. DE Patent 2045111. Chemical Abstract, 1971:74:141839.
16. Butula I., Ruzdija A., Kalmar J. New synthesis of phthalazine-1- hydrazinone Croat. Chem. Acta, 1979:52:43–45.
17. Sangshetti N.J., Khan F.A,K., Chouthe R., Zaheer Z., Ahmed R. Water-mediated oxalic acid catalysed one-pot synthesis of 2-(substituted phenyl) phthalazin-1(2H)-ones. Journal of Taibah University for Science, 2015:9:548–554.
18. Kessler S., Wegner H. One-pot synthesis of phthalazines and pyridazino-aromatics: a novel strategy for substituted naphthalenes. Organic Letters, 2012:14:3268–3271; (b) Wang L., Zhou X., Xiao M., Jiang N., Liu F., Zhou W. Synthesis and biological evaluation of substituted 4-(thiophen-2-ylmethyl)-2H-phthalazin-1-ones as potent PARP-1 inhibitors. Bioorganic & Medicinal Chemistry Letters, 2014:24 (16):3739–3743.
19. Sato H., Horie S., Sekikawa N., Ono H. DE Patent 2632656. Chemical Abstract, 1977: 86:171487.
20. Hirayama T., Kamada M. JP Patent 52027785. Chemical Abstract, 1977:87:184540.
21. Sutherland J.B., Freeman J.P., Williams A.J. Biotransformation of isoquinoline, phenanthridine, phthalazine, quinazoline and quinoxaline by Streptomyces viridosporus. Applied Microbiology and Biotechnology, 1998:49:445–449.
22. Sugimoto A., Sakamoto K., Fujino Y., Takashima Y., Ishikawa M. Synthesis and inhibitory effect on platelet aggregation of 2-phenyl-1(2H)-phthalazinone derivatives. Chem Pharm Bull, 1985:33 (7):2809–2820.
23. Sangshetti J.N., Lokwani D.K., Chouthe R.S., Ganure A., Raval B., Khan F.A.K. Green synthesis and biological evaluation of some new benzothiazolo [2,3-b] quinazolin-1-ones as anticancer agents. Medicinal Chemistry Research, 2014:23:4893–4900.
24. Khan F.A.K., Zaheer Z., Sangshetti J.N., Ahmed R.Z. Facile one-pot synthesis, antibacterial activity and in silico ADME prediction of 1-substituted-1H-1,2,3,4-tetrazoles. Chemical Data Collections, 2018:15-16:107-114.
25. Lipinski C., Lombardo F., Dominy B., Feeney P. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 2012:46:4-17.
26. Molinspiration. Molinspiration Chemoinformatics. http://www.molinspiration.com/cgi-bin/properties. 2021.
27. Zhao Y., Abraham M., Le J., Hersey A., Luscombe C., Beck G. Rate-limited steps of human oral absorption and QSAR studies. Pharm Research, 2002:19:1446-57.
28. Morgan D., Ollisa W.D., Stanforth S. Preparation and cycloaddition reactions of novel heterocyclic mesomeric betaines. Tetrahedron, 2000:56(30):5523–5534.
29. Outerbridge V., Landge S., Tamaki H., Torok B. Microwave-promoted solid-acid-catalyzed one-pot synthesis of phthalazinones. Synthesis, 2009,11:1801–1806.
30. Peters A.T., Pringle G.T., Rowe F.M. A reaction of diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXIV. The phthalazine reaction with bases not containing a nitro-group. Derivatives of halogenobenzene-2-naphthol-1-diazosulphonates. Journal of the Chemical Society, 1948:2:597–601.
31. Brodrick C.I., Peters A.T., Rowe F.M. A reaction of certain diazosulphonates derived from β-naphthol-1-sulphonic acid. Part XXV. The phthalazine reaction with bases not containing a nitro-group. Derivatives of 2'-chlorobenzene-2-naphthol-1-diazosulphonate. Journal of the Chemical Society, 1948:2:1026–1029.
32. Heravi M.M., Baghernejad B., Oskooie H. A novel method for the synthesis of 1(2H)-phthalazinones using silica-supported perchloric acid. Journal of Heterocyclic Chemistry, 2009:46(2):351–354.

33. Kuznetsov V., Shubin K., Schipalkin A., Petrov M. Efficient route to benzo[4,5]imidazo[2,1-a]phthalazines. Tetrahedron, 2006:62 (42):10018–10030.
34. Cracknell M.E., Goodland M., McOmie J.F.W. Benzocyclobutenes. Part 8. Geometrical isomerism of arylhydrazones of benzocyclobutene-1,2-dione. Bulletin of the Chemical Society of Japan, 1983:56(3):965–966.
35. Ertl P., Rohde B., Selzer P. Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. Journal of Medicinal Chemistry, 2000:43(20):3714-17.