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Ammonium chloride mediated synthesis of 2-aryl-phthalazinone from *O*-formyl benzoic acid and in silico applications

Avinash M. Patil,[a] Priyanka M. Lagad,[a] Bhavana Soge,[a] Rohan Meshram,[a] Mahendra N. Lokhande,[b]* and Pradeep D. Lokhande[a]*

[a] *Department of Chemistry, Savitribai Phule Pune University, Ganeshkhind, Pune-411007, India*
[b] *Department of Chemistry, Avvaiyar Government College for Women Karaikal, Puducherry (U.T.) 609602, India*
Email: mnlok@dhtepdy.edu.in; pdlokhande@gmail.com

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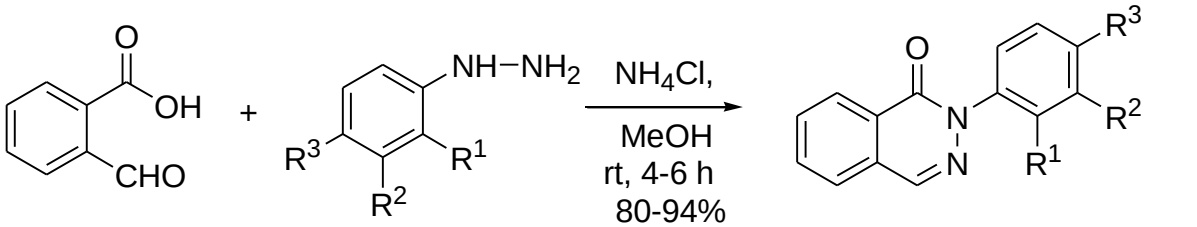
Abstract

Ammonium chloride mediated cyclization reaction leading to one-pot synthesis of 2-arylphthalazinone from 2-carboxyl benzoic acid and aryl hydrazine in methanol was developed. This method was found to be tolerant of a broad range of functional groups. This novel protocol features mild reaction conditions, operational simplicity, and easy availability of starting material and very high yields. The molecular docking data indicates that compound have comparable free energy with the standard compound. They interact only with some conserved residues such as Leu387, Trp387, Phe381, Tyr385. Therefore, this compound can be considered for further analysis and they have enormous potential to be tested experimentally



R^1= H, Me, R^2 = H, NO_2,
R^3 = H, F, Cl, Br, CN,COOH

Keywords: Ammonium chloride; aldehyde; phenylhydrazine; *O*-formyl benzoic acid; phthalazinone

Introduction

Phthalazinone has occupied a unique position in the design and synthesis of novel bioactive agents that exert remarkable medicinal activities. Synthetic chemistry of phthalizinone is more important due to its broad range of biological activities they possess, including antidiabetic, anticancer, analgesic, antiasthmatic, antimicrobial, antidepressant, antihypertensive and anti-inflammatory agents **Fig.** 1.[1] Zopolrestat **i** is a potent aldose reductase inhibitor for chronic diabetes which showed good oral absorption and high blood level favorably long plasma half-life. It is in clinical trials.[2] Aurora kinases ii (consisting of auroras A, B and C) have a crucial role in the cellular division being over-expressed in diverse solid tumors particularly in aurora A.[3] The naturally occurring azelastine iii is the second generation selective H1R antagonist which is recommended typical for the antihistamine therapy as allergic rhinitis.[4] The 4-(3,4-dimethoxyphenyl)-2H-phthalazin-1-ones iv were synthesized and tested against PDE3 and PDE4 enzymes.[5] A 5-arylamino-1,2,4-thiadiazole v linked at N-2 of the phthalazinone nucleus by a methyl or ethyl chain shows activity against Bacillus subtilis (Gram-positive bacteria) and yeast-like fungi as Candida albicans and Candida parapsilosis.[6] Also Various phalazinone derivatives v and vi are widely used as catalyst for asymmetric dichlorinatiom, halolactonization and different thermo physical properties.[7-9] Because of the diverse properties physiochemical of phthalizinone derivatives they have received increasing interest in exploring straight forward methods for their syntheses. Recently few papers were published on the synthesis of the 2-Arylphthalazin-1(2H)-ones, which include reactions of o-phthalaldehyde and phenylhydrazines of bromo derivatives,[10] o-nitrophenylhydrazines through different 2-(2-nitrophenyl)-1,2-dihydro-1-phthalazinones,[11] $HClO_4$-SiO_2 catalyzed reactions of phthalaldehydic acid with phenyl hydrazines,[12] montmorillonite K-10 effectively catalyzed the condensation in microwave,[13] using Pt-nanowires as catalysts,[14] and thiazolyl-phthalazinediones under ultrasound irradiation,[15] and a metal free reaction with atom economic reactions were reported,[16] looking at importance of 2-Arylphthalazin-1(2H)-ones nuclear moiety. Instead of use of the unstable catalyst and a transition metal-containing activator-like copper iodide (CuI) or use of expensive transition metal containing catalyst like ultrathin platinum nanowires and palladium containing such as $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and $Pd(THF)_2$ and use of high temperatures (150-160 °C), use used easy available ammonium chloride mediated synthesis of 2-Aryl-Phthalazinone from o-Formyl benzoic acid. Therefore, the development of efficient and convenient methods is highly desirable. Earlier we have reported synthesis of variety of heterocyclic including substituted pyradiazine. Recently we have reported ammonium chloride mediated synthesis of a 3-arylamino and 3-indolylphthalides, a 5-membered heterocyclic ring, by the cyclization of o-carbaldehyde benzoic acid and anilines and indoles in methanol.[17] As a part of this work, we were interested in the reaction between o-carbaldehyde benzoic acid and aryl hydrazines. In this work we report on a convenient synthesis of 2-aryl phthalazinone that is based on the reaction between o-carbaldehyde benzoic acid and aryl hydrazine. Ammonium chloride is a useful reagent in organic synthesis. It is an inexpensive, nontoxic, soluble in water and hence it is easily separated out, readily available reagent and because of these economical properties it is used for several transformations in organic synthesis.[18] In continuation of previous work, we used ammonium chloride for the synthesis of phthalazinone.

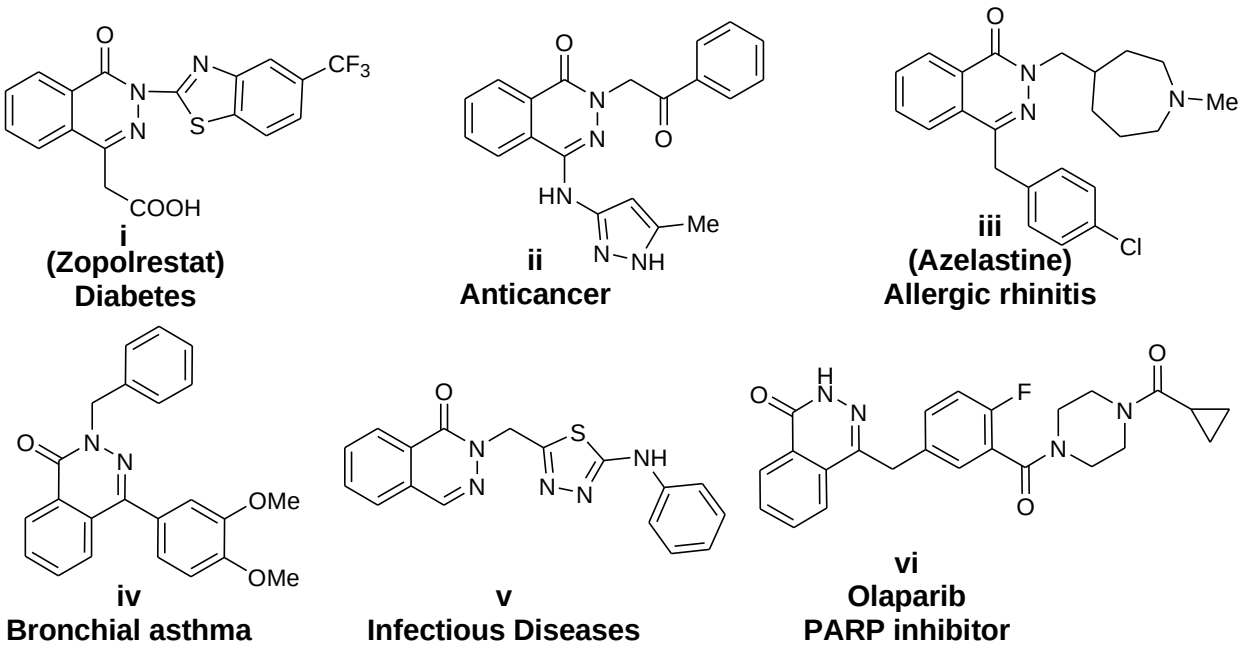


Figure 1. Numerous phthalazinone derivatives with relevant therapeutic applications.

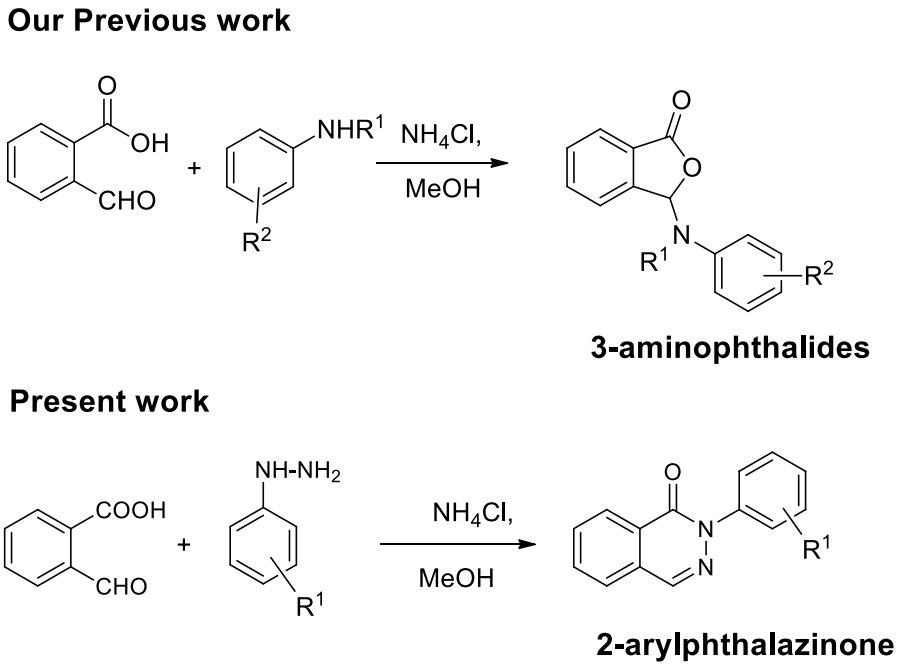


Figure 2. Synthesis of a 3-arylaminophthalides arylamino and 3-indolylphthalides, a 5- membered heterocyclic ring.

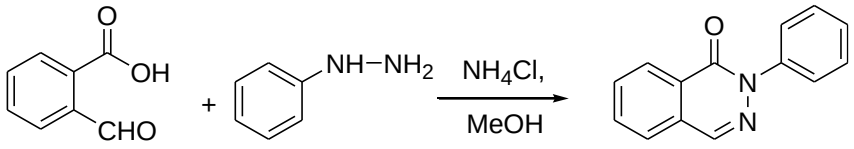
Results and Discussion

We reported the synthesis of 3-aminophthalides and found that some of these molecules have a good biological activity against tuberculosis bacteria. In general, an amino group and nitrogen heterocyclic in a drug

molecule exhibits potentially good biological activity. It was envisaged that possession of one more amino group in a 3-aminophthalides will enhance the activity of 3- aminophthalides. Hence instead of aniline derivatives and indoles we extended the reaction of 2-carboxylbenzaldehydes with phenyl hydrazine by a similar procedure used for the synthesis of 3-aminopthalide. Thus 2-carboxybenzaldeyde **1a** reacted with phenyl hydrazine **2a** in presence of ammonium chloride 0.1 equivalent in methanol. The reaction shows no further changes, as monitored by TLC, after 5 hours at room temperature. The product was separated and purified on column chromatography. The product was obtained as colorless solid with 39 % yield and mp is 74 ^{o}C. Product **3a** was characterized by spectroscopic analysis showing presence of strong band at 1652 cm^{-1} indicating it could be of lactams rather than carbonyl group of lactones in phthalides. The formation of a cyclic lactams was supported by NMR spectroscopy as compound **3a** exhibited a signal at 8.55 as singlet corresponding to the proton of C-H at 4-position in cyclic amide moiety and its ^{13}C-NMR spectrum showed a peak at 158 corresponding to carbonyl carbon of lactam moiety. The detailed spectral analysis confirmed the formation of 2-phenylthalazine 1-(2H)-One, spectral analysis with the reported compound.[13] It is assumed that the reaction starts with the condensation between aldehyde **1a** and phenyl hydrazine **2a** to give hydrazone as an intermediate in presence of Lewis acid ammonium chloride in methanol. In the second step hydrazone undergoes intermolecular cyclization to yield the 2-phenyl phthalazinone.

To facilitate the condensation and cyclization reaction in order to improve the yields, we decided to run the transformation by increasing the equivalents of Lewis acid ammonium chloride. When 0.25 equiv. of ammonium chloride was added the product **3a** obtained in 78% yield at room temperature (Table 1, entry **b**). The process of condensation and intra-molecular cyclization was improved by a subsequent increase in the proportional amount of ammonium chloride at room temperature and the corresponding phthalazinone was isolated with 91% yield (Table 1, entry c) than entry e as as long reaction time will not bring a major variable change. Increase the amount of ammonium chloride up to 1.00 equivalents gave 87% yield (Table 1, entry **d**). Additionally, when the amount of ammonium chloride was 0.5 equivalents duration for reaction up to 8h and **3a** was obtained without improved yield (Table 1, entry **e**). Then we increased the temperature up to 60 ^{o}C for 0.5 equivalents of ammonium chloride gave 81% yield. No prominent increases in yield even by increases the temperature by 20 ℃ for 0.5 equiv. ammonium chloride.

Table 1. Optimization of reaction condition.[a]



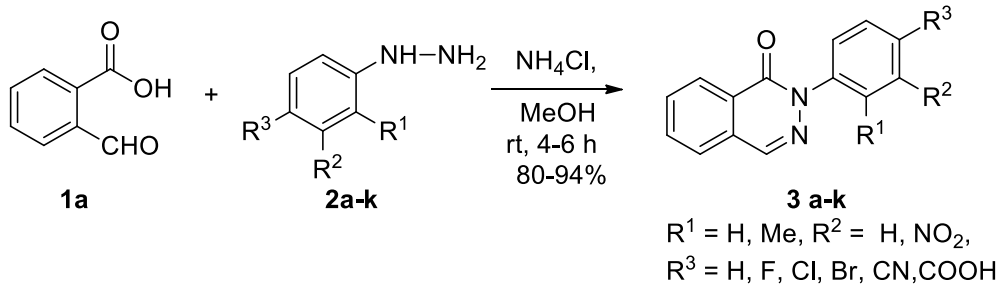
1a **2a** **3a**

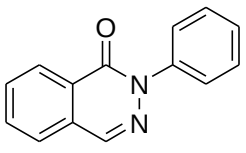
Entry	NH_4Cl (equivalent)	Temp (^{o}C)	Time (h)	Yield (%) (**3a**)
a	0.10	rt	5	39
b	0.25	rt	5	78
c	0.50	rt	5	91
d	1.00	rt	5	87
e	0.50	rt	8	86
f	0.50	60	5	81

g	0.50	>60	5	79

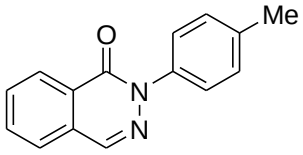
Next the influence of the various solvent on the outcome of the model reaction was studied. It was observed that I can be run in protic and aprotic solvents such as dimethyl sulphoxide, ethanol, dimethylformamide, diethyl ether, dichloromethane, benzene and diphenyl ether were analyzed. In protic solvents yields are better than some protic solvents. The methanol was found to be an effective solvent for condensation and intra-molecular cyclization. It should be noted that ethanol, DMSO, DMF, the yields are in same range. There is no phathlazinone formation in absence of solvent. Under optimized conditions in hand we explored the scope of the condensation and cyclization process for different substituted aryl hydrazines hydrazines (**Table 2**). The substituent's such as methyl, dimethyl, chloro, fluoro, bromo, nitrile, carboxyl and hydrazide of pyridine were studied. Yields of the corresponding phthalazinones were in the range between 80-94%. It should be noted that yields with aryl hydrazines carrying with the electron donating substituent was higher than the yield observed with aryl hydazines carrying with electron withdrawing substituent. In addition, it was studied whether 2-methyl substituted group in phenyl hydrazine exhibited any steric influence on the product formation, but the yield of 2,4-disustituted methyl substituted aryl hydrazine resulted in the highest 94% yield in the studied aryl hydrazines. While studying the biological activities of 3-amino phthalides, we observed that some of these molecules exhibited activities against tuberculosis bacteria. Hence, we are attracted towards synthesis of phthalazinone containing pyridyl hydrazide that is ionized **4a** which has -$CONHNH_2$ group. Thus isoniazid was reacted with 2-carboxylbenzaldeyde under optimized conditions. To our gratitude we obtained a phthalazinone containing ionized functionality in very high yields **5a**, 83% comparable with the other electron withdrawing groups. The carbonyl group of hydrazide in pyridine does not influence the yield of the products.

Table 2. Synthesis of 2 arylphthalazin-1(2H) ones using ammonium Chloride.

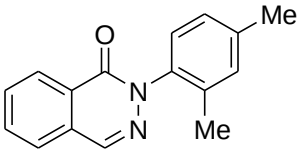




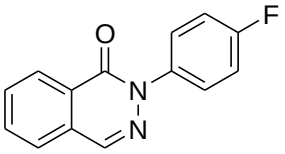
3a, 5 h, 91%



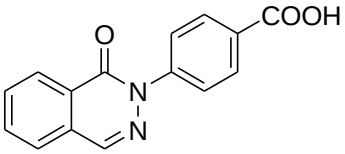
3b, 5 h, 92%



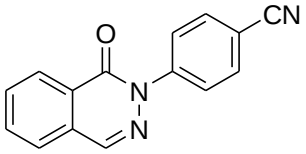
3c, 5 h, 94%



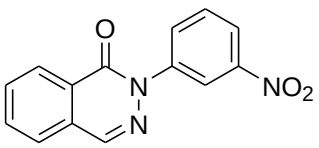
3d, 5 h, 85%



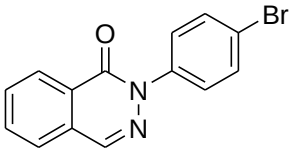
3e, 4 h, 81%



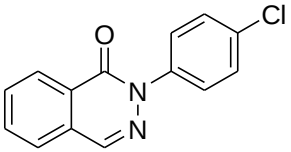
3f, 4 h, 80%



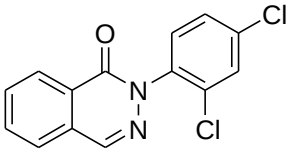
3g, 4 h, 81%



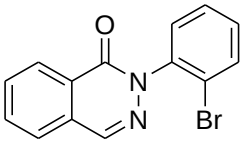
3h, 5 h, 83%



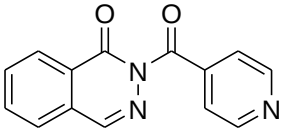
3i, 5 h, 82%



3j, 4 h, 80%

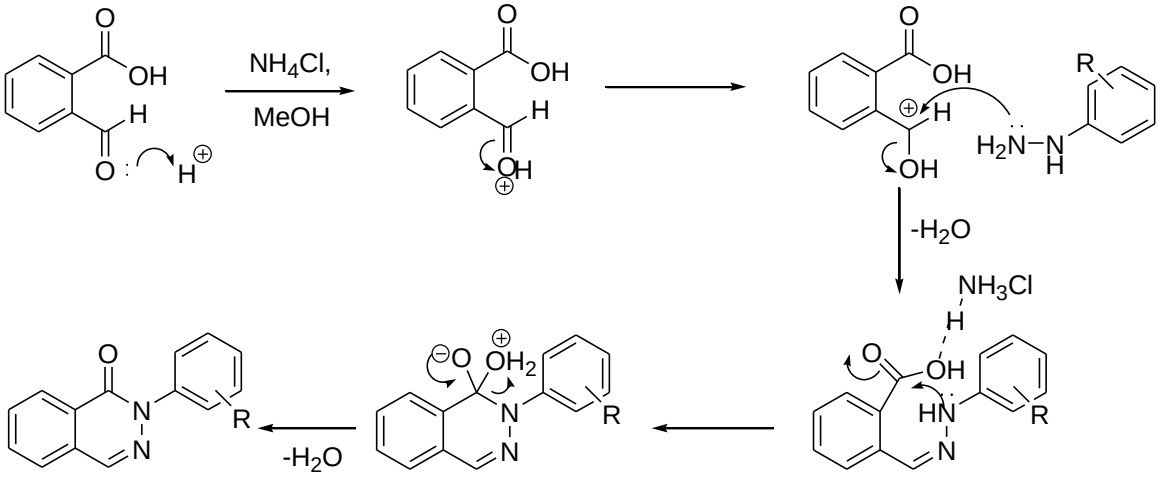


3k, 5 h, 83%



5a, 6 h, 83%

While studying the biological activities of 3-amino phthalides, we observed that some of these molecules exhibited activities against tuberculosis bacteria. Hence, we are attracted towards synthesis of phthalazinone containing pyridyl hydrazide that is isoniazid **4a** which has the -$CONHNH_2$ group. Thus isoniazid was reacted with 2-carboxylbenzaldeyde under optimized conditions. To our gratitude we obtained a phthalazinone containing isoniazid functionality in very high yields **5a**, 83% comparable with the other electron withdrawing groups. The carbonyl group of hydrazide in pyridine does not influence the yield of the products.



Scheme1. Possible reaction mechanism for the Synthesis of Phthalazinones using NH_4Cl.

With respect to the reaction mechanism, it is assumed that the first step is condensation between the formyl group substrate phthalaldehydic acid and amino group of phenyl hydrazine to give hydrazine. The hydrazine could not be isolated. Stirring continues for 4-6 hours. The structures are unambiguously confirmed by NMR spectroscopy.

In silico Analysis:

Table 3: The binding free energy of Aldose Reductase and COX-II in Kcal/mol is calculated and mentioned.

Sr.No.	Compound Code	Binding Free Energy (Kcal/mol)	
		Aldose Reductase	COX-II
1	3a	-8.53	-7.25
2	3b	-8.8	-7.69
3	3c	-8.75	-7.97
4	3d	-8.51	-7.3
5	3e	-8.06	-7.8
6	3f	-8.93	-7.59
7	3g	-8.83	-8.99
8	3h	-9.03	-7.95
9	3i	-8.87	-7.79
10	3j	-8.52	-7.98
11	3k	-8.02	-7.63
12	3l	-8.74	-7.22
	Zopolrestat*	-10.75	--
	Naproxen*	--	-8.87

The minimum binding free energy of a compound is considered of the most stable compounds. If the error value is included with respect to the reference; the margin of the compound considered 2 kcal/mol. It is seen that, all the values of the compound obtained is closer to the references of the enzyme. As per the information present in the **table 3** 3h is found to be the most stable compound in reference to the enzyme Aldose Reductase inhibitor (-9.03 kcal/mol). **3g** is found to be the most stable compound in reference to the enzyme COX-II inhibitor (-8.99 kcal/mol). When we considered both the enzyme (i.e. Aldose Reductase and COX-II) the binding energy of compound **3g** (-8.83 kcal/mol, -8.99 kcal/mol) and 3j (-8.52 kcal/mol, -7.98 kcal/mol) is found to be compatible.[19,20]

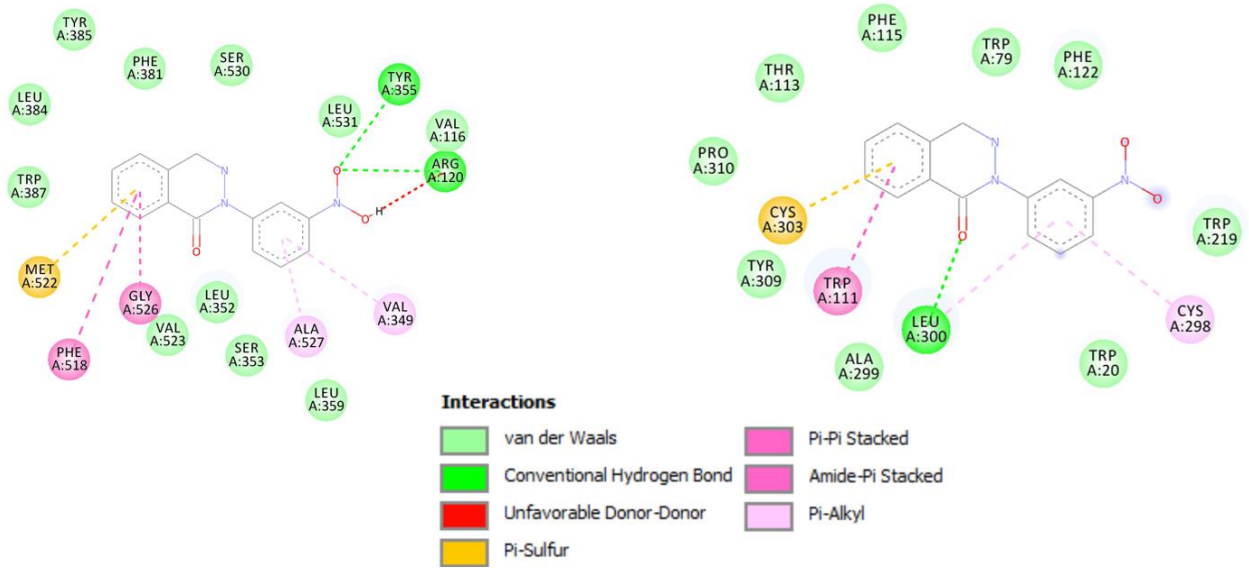


Figure 1: COX3g

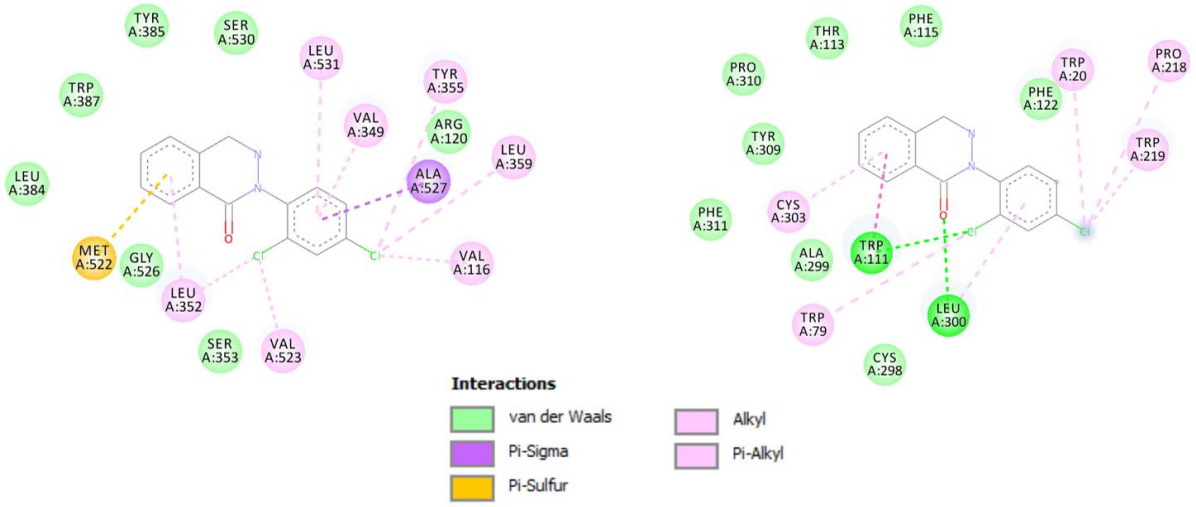


Figure 2: COX3j

Both the interactions above shows have common interactions which make them stable such as Van der waals, Pi-Sulphur and Pi-Alkyl. And also there are different interactions which are essential such as Pi-Sigma, Conventional Hydrogen bond, Alkyl etc

Conclusions

We have developed a convenient and efficient method for synthesis of 2-arylphthalzinone using ammonium chloride in methanol. It is a metal, strong acid, metal Lewis acid free economical method resulting in the very high yields. The formation and cyclisation of hydrazones with ammonium chloride is quite fast at room temperature and affords corresponding products. The mild reaction condition, operational simplicity and use of readily available reagents, affords a convenient one step method with utility in medicinal chemistry. As per the results of binding energy it has been found that compound **3g** and **3j** can act as inhibitors of both the enzymes Aldose Reductase and COX-II. They are found to be more stable due to interactions with some conserved residues. Out of all the molecules we found **3g** and **3j** to have the best binding free energy and have been found that these compounds have stabilized interactions.

Experimental Section

Synthesis of phthalazinone derivatives

In the round bottom flask was added 2-carboxylbenzaldehyde (1.5 g, 1 mmol) phenyl hydrazine hydrochloride (1.08 g, 1 mmol) and ammonium chloride (0.026g, 0.5 mmol) in 15mL methanol. The reaction was stirred for 4.5-6 h room temperature. The precipitate formed and completes the reaction is monitored by TLC. The product was filtered, rinsed with cold methanol and purified by crystallization in ethanol or 100-200 silica in petroleum ether and ethyl acetate as solvent system.

2-Phenylphthalazin-1(2H)-one (3a). Pale yellow (202 mg, 91% yield); mp 104 ℃ (lit.[13] 104-105℃); IR (cm^{-1}): 1652, 1452, 1058; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.31 (d, *J* 7.8 Hz, 1H), 8.03-7.94 (m, 2H), 7.92-

7.85 (m, 1H), 7.61 (d, *J* 7.8 Hz, 2H), 7.51 (t, *J* 7.7 Hz, 2H), 7.41 (t, *J* 7.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO): δ 158.27, 141.85, 138.70, 133.91, 132.32, 129.23, 128.52, 127.66, 127.52, 126.97, 126.18, 125.98; MS (70 ev) *m/z*: 223 (M^+ H).

2-(*p*-Tolyl)phthalazin-1(2*H*)-one (3b). Brown oil (217 mg, 92% yield); IR (cm^{-1}): 1657, 1324;^{1}H NMR (400 MHz,DMSO-d_6): δ 8.54 (s, 1H), 8.31 (d, *J* 7.8 Hz, 1H), 8.01-7.94 (m, 2H), 7.93-7.86 (m, 1H), 7.47 (d, *J* 8.3 Hz, 2H), 7.30 (d, *J* 8.2 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.28, 139.44, 138.56, 136.93, 133.82, 132.27, 129.22, 128.96, 127.66, 126.93, 126.16, 125.74, 20.65;HRMS (ESI-qTOF) Calculated for $C_{15}H_{12}N_2O$ $[M+H]^+$: 237.1028 found 237.1033.

2-(2,4- Dimethylphenyl)phthalazin-1(2*H*)-one (3c). Brown solid (235 mg, 94% yield); IR (cm^{-1}): 1657, 1484, 763, 685; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53 (s, 1H), 8.30 (d, *J* 7.9 Hz, 1H), 7.98 (tt, *J* 7.9, 3.9 Hz, 2H), 7.90 (ddd, *J* 8.4, 6.7, 1.9 Hz, 1H), 7.24-7.15 (m, 2H), 7.13 (d, *J* 7.9 Hz, 1H), 2.33 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.25, 138.70, 138.49, 137.94, 134.41, 133.85, 132.27, 130.99, 129.48, 127.53, 127.51, 127.10, 127.03, 126.05, 20.64, 17.04; HRMS (ESI-qTOF) Calculated for $C_{16}H_{14}N_2O$ $[M+H]^+$:251.1089 found 251.1088.

2-(4-Fluorophenyl)phthalazin-1(2*H*)-one (3d). Brown solid (204 mg, 85% yield); mp 156-158 ℃ (lit.[11] 158.6 ℃); IR (cm^{-1}): 1652, 1502, 1142; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* 7.6 Hz, 1H), 8.30 (s, 1H), 7.93-7.60 (m, 5H), 7.19 (t, *J* 8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.99, 159.27, 138.67, 138.02, 133.69, 132.18, 129.57, 128.55, 127.66, 127.57, 127.33, 126.30, 115.78, 115.55; MS (70 ev) *m/z*: 241 (M^+ H).

4-(1-Oxophthalazin-2(1*H*)-yl)benzoic acid (3e). Pale yellow solid (215 mg, 81% yield); IR (cm^{-1}): 3300, 2829, 1666, 1293; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (s, 1H), 8.29 (d, *J* 7.8 Hz, 1H), 8.04 (d, *J* 8.6 Hz, 2H), 7.98-7.82 (m, 3H), 7.74 (d, *J* 8.6 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.10, 158.72, 145.49, 139.56, 134.35, 132.72, 129.95, 129.77, 129.36, 127.81, 127.30, 126.57, 125.83; MS (70 ev) *m/z*: 267 (M^+ H).

4-(1-Oxophthalazin-2(1*H*)-yl) benzonitrile (3f). Brown solid (198 mg, 80% yield); mp168 ℃; IR (cm^{-1}): 1690, 2214; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, *J* 7.7 Hz, 1H), 8.28 (s, 1H), 7.89- 7.78 (m, 2H), 7.75 (d, *J* 7.8 Hz, 1H), 7.67-7.62 (m, 2H), 7.45 (d, *J* 8.7 Hz, 2H); MS (70 ev) *m/z*: 248 (M^+ H).

2-(4-Bromophenyl) phthalazin-1(2*H*)-one (3h). White solid (249 mg, 83% yield); mp 168-170 ℃ (lit[13] 170 ℃); 80%; IR (cm^{-1}): 1654, 1329; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* 7.6 Hz, 1H), 8.31 (s, 1H), 7.97-7.70 (m, 3H), 7.63 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.19, 141.02, 138.91, 133.80, 132.28, 131.92, 129.55, 128.58, 127.44, 127.34, 126.36, 121.39; MS (70 ev) *m/z*: 300 (M^+).

2-(4-Chlorophenyl) phthalazin-1(2*H*)-one (3i). Brown solid; (210 mg, 82% yield); mp 171 ℃ (lit.[11] 169.8 ℃); IR (cm^{-1}): 1656, 1240; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, *J* 7.7 Hz, 1H), 8.31 (s, 1H), 7.95-7.91 (m, 2H), 7.89-7.81 (m, 2H), 7.78-7.73 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.17, 145.48, 139.52, 134.14, 132.66, 132.54, 129.34, 127.50, 126.49, 125.95, 118.56, 110.90; MS (70 ev) *m/z*: 257 (M^+ H).

2-(2-Bromophenyl)phthalazin-1(2*H*)-one (3k). White solid (249 mg, 83% yield);IR (cm^{-1}): 1658, 1334, 762; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, *J* 7.8, 0.7 Hz, 1H), 8.29 (s, 1H), 7.84 (dtd, *J* 16.5, 7.4, 1.3 Hz, 2H), 7.79-7.71 (m, 2H), 7.51 – 7.43 (m, 2H), 7.33 (ddd, *J* 8.1, 6.1, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.02, 141.14, 138.74, 133.82, 133.61, 132.17, 130.46, 129.90, 129.56, 128.57, 128.41, 127.32, 126.48, 122.11; MS (70 ev) *m/z*: 301 (M^+ H).

2-Isonicotinoylphthalazin-1(2*H*)-one (5a). White solid (208 mg, 83% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.78 (d, *J* 5.9 Hz, 2H), 8.09 (d, *J* 7.5 Hz, 1H), 7.92 (dd, *J* 7.8, 0.9 Hz, 1H), 7.86 (dd, *J* 4.5, 1.5 Hz, 2H), 7.65 (t, *J* 7.7 Hz, 1H), 7.54 (t, *J* 7.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.06, 161.83, 150.35, 147.86, 140.40, 134.41, 132.04, 130.79, 130.41, 129.86, 126.78, 121.65; MS (70 ev) *m/z*: 251 (M^+).

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References

1. Vila, N.; Besada, P.; Costas, T.; Costas-Lago, M. C.; Teran. C. *Eur. J. Med. Chem.* **2015**,*97*, 462-482. https://doi.org/10.1016/j.ejmech.2014.11.043
2. Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. *J. Med. Chem.* **1991**, *34*, 108-122. https://doi.org/10.1021/jm00105a018
3. Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; Saal, W.V.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth *M. J. Med. Chem*. **2011**, *54*, 312-319. https://doi.org/10.1021/jm101346r
4. Slack, R. J.; Hart, A. D.; Luttmann, M. A.; Clark, K. L.; Begg, M. *Eur. J. Pharmacol.* **2011**, *670*, 586-592. https://doi.org/10.1016/j.ejphar.2011.09.017
5. Mey, M. V.; Hatzelmann, A.; Laan, J. G.; Sterk, G. J.; Thibaut, U.; Timmerman, H. *J. Med. Chem.* **2001**, *44*, 2511-2522. https://doi.org/10.1021/jm010837k
6. Onkol, T.; Dogruer, D. S.; Uzun, L.; Adak, S.; Ozkan, S.; Sahin, M. F. J. *Enzyme Inhib. Med. Chem.* **2008**, *23*, 277-284. https://doi.org/10.1080/14756360701408697
7. Cashman, J. R.; Voelker, T.; Zhang, H. T.; O'Donnell, J. M. *J. Med. Chem.* **2009**, *52*, 1530-1539. https://doi.org/10.1021/jm8010993
8. Zak, S.B.; Gilleran, T.G.; Karliner, J.; Lukas, G. *J. Med. Chem.* **1974**, *17*, 381-382. https://doi.org/10.1021/jm00249a035
9. Dogruer, D. S.; Kupeli, E.; Yesilada, E.; Sahin M. F. *Arch. Pharm. Med. Chem*. **2004**, *337*, 303-310. https://doi.org/10.1002/ardp.200200719
10. Sugimoto, A. ; Sakamoto, K. ; Fujino, Y. ; Takashima, Y. ; Ishikawa, M. *Chem. Pharm. Bull.* **1985**,*33*, 2809-2820. https://doi.org/10.1248/cpb.33.2809
11. Kuznetsov, V.A.; Shubin, K. M.; Schipalkin, A. A.; Petrov, M. L. *Tetrahedron* **2006**, *62*,10018–10030. https://doi.org/10.1016/j.tet.2006.07.089
12. Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. *J. Heterocycl. Chem.* **2009**,*46*, 351-354. https://doi.org/10.1002/jhet.77
13. Outerbridge, V. M.; Landge, S. M.; Tamaki, H.; Török B.; *Synthesis* **2009**, *11*, 1801-1806. https://doi.org/10.1055/s-0028-1088074
14. Shi, L.; Hu, L.; Wang, J.; Cao, X.; Gu, H. *Org. Lett.* **2012**, *14*, 1876–1879. https://doi.org/10.1021/ol300471a
15. Elsharabasy, F. S.; Gomha, S. M.; Farghaly, T. A.; Elzahabi, H. S. A. *Molecules* **2017**, *22*, 319.

https://doi.org/10.3390/molecules22020319

16. Patil,S.; Duggal,H.; Bagul. K. T.; Kamble, S.; Lokhande, P.; Gacche, R.; Meshram, R. *Comb. Chem. High Throughput screen.* **2020**, *23*,723-739. https://doi.org/10.2174/1386207323666200422082754
17. Lu, B; Xie, Z; Lu, J; Liu, J; Cui, S.; Ma, Y.; Hu, X; Liu, Y; Zhong, K. *ACS Sustainable Chem. & Eng.* **2019,** 7,134-138. https://doi.org/10.1021/acssuschemeng.8b05657
18. Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett*. **2004**, *6*, 4771-4774. https://doi.org/10.1021/ol0479388
19. Kadam, A. ; Dawane, B. ; Pawar, M. ; Shegokar, H. ; Patil, K. ; Meshram, R. ; Gacche, R. *Bioorg. Chem.* **2014**, *53*,67-74. https://doi.org/10.1016/j.bioorg.2014.02.002
20. Meshram, R.J. ; Baladhye, V.B. ; Gacche, R.N. ; Karale, B.K. ; Gaikar, R.B. *J Clin. Diagn Res.* **2017** *11*, KF01-KF08. https://doi.10.7860/JCDR/2017/22761.9925