Original Article: Simple, Highly Efficient Synthesis 2-Amino-4-phenyl-4,5,6,7-tetrahydropyrano[3,2-c]carbazole-3-carbonitrile Derivatives Using Silica Supported Dodeca-Tungstophosphoric Acid DTP/SiO_2

Sunil Gaikwad[a,*] |Murali Venkata Basavanag Unnamatla[b]

[a]*Department of Chemistry, Dr. D.Y. Patil Arts Commerce and Scienec Womens College Pimpri, Pune-411018, India*
[b]*Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM. Carretera Toluca-Atlacomulco Km 14.5, Toluca, Estado de México, 50200, México. Universidad Autónoma del Estado de México*
[b]*Facultad de Química, Universidad Autónoma del Estado de México, Carretera Toluca-Atlacomulco Km 14.5, Unidad San Cayetano, Toluca, Estado de México, C. P. 50200 México*

Use your device to scan and read the article online

Citation S. Gaikwad*, M.V.B. Unnamatla, **Simple, Highly Efficient Synthesis 2-Amino-4-phenyl-4,5,6,7-tetrahydropyrano[3,2-c]carbazole-3-carbonitrile Derivatives Using Silica Supported Dodeca-Tungstophosphoric Acid DTP/SiO_2**. *J. Appl. Organomet. Chem.*, **2022**, *2*(1), 24-30.

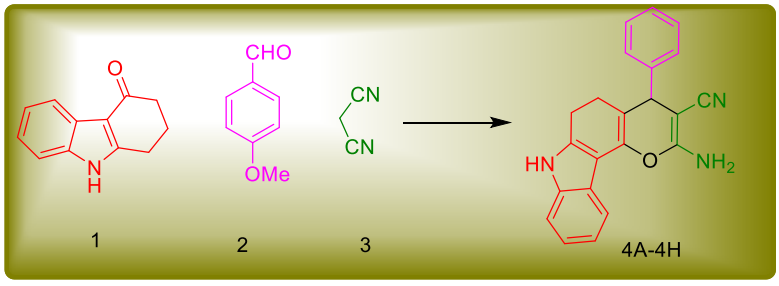
https://doi.org/10.22034/jaoc.2022.332760.1049

Article info:
Received: 06-03-2022
Accepted: 31-03-2022
Available Online: 02-04-2022
ID: JAOC-2203-1049
Checked for Plagiarism: Yes
Peer Reviewers Approved by:
Dr.Fatemeh Mohajer
Editor who Approved Publication:
Professor Dr. AbdelkaderZarrouk

Keywords:
DTP/SiO_2, Greener solvent, one-pot multicomponant, carbazole-3-carbonitrile

ABSTRACT

The one-pot multicomponent efficient and easily operational protocol has been developed for the synthesis of tetrahydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives. The methods work via the multicomponent reaction between 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one , aldehyde and malononitrile catalyzed by the silica-supported dodeca tungstophosphoric acid (DTP/SiO_2) catalyst. The protocol is practically green, milder reaction condition, higher yield, with short reaction times and recyclability of the catalyst.



Introduction

The heterocyclic chemistry and their pharmacological application is the key connection of the molecules for their wild range of biological application[1]. There are many heterocyclic moieties in nature having a range of biological properties among them

***Corresponding Author:** Sunil Gaikwad(sunilunipune2012@gmail.com)*

pyranopyrazoles are significant scaffolds because of a broad range of medicinal properties like anti-inflammatory [2], anticancer[3] and analgesic[4] antimicrobial [5], antiplatelet [6], anti-inflammatory [7-8], antitumor [9,10], analgesic [11], molluscicidal [12], cholinesterases inhibitory activity [13], vasodilator [14], and human Chk1 kinase inhibiting activity [15] therefore the synthesis of their analogs has valuable important in the pharmaceutical chemistry. Besides this PY scaffolds have also important in the field of agrochemistry because of their herbicidal fungicidal and bactericidal properties, [16,17]. Therefore, for the preparation of PY moiety has a great interest in the research for finding novel derivatives. The dihydropyrano[2,3-c]pyrazole molecule is a significant intermediate that exists in four isomeric forms with a high bioactive profile (**Figure 1**.).

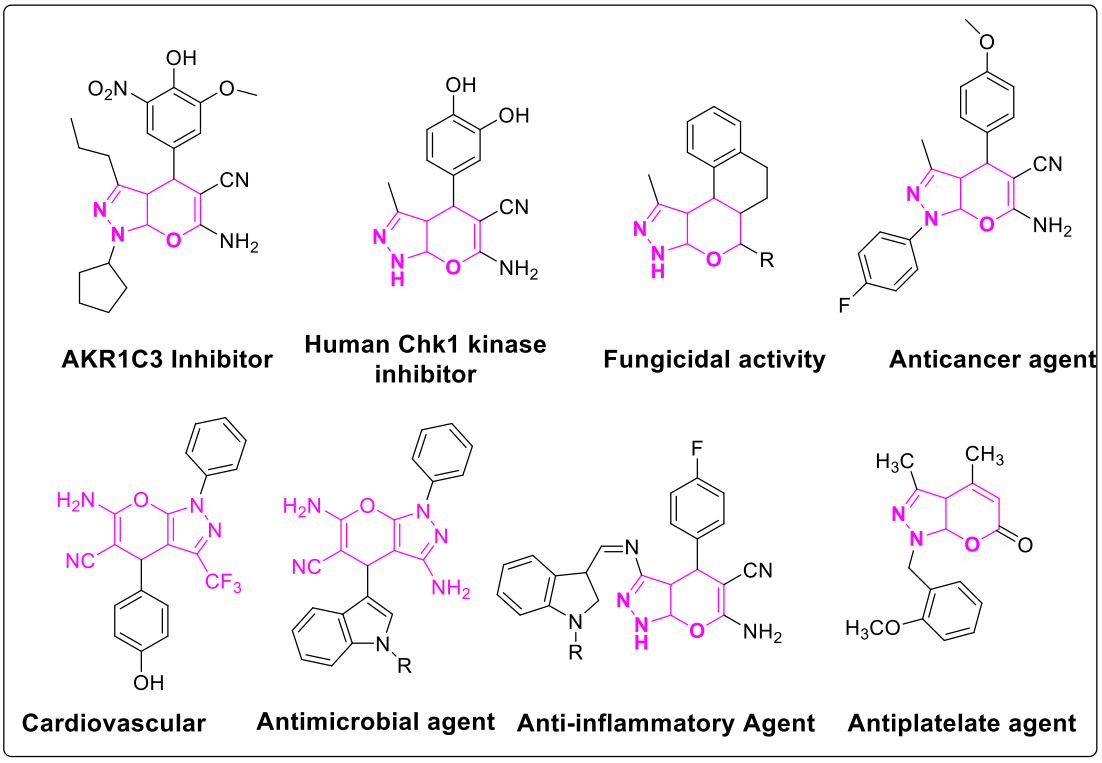


Figure 1. Bioactive dihydropyrano[2,3-c]pyrazole agent

As per the pharmaceutical importance of pyranopyrazole, the various synthetic protocols have been described for the preparation of bioactive modified medicinal active heterocyclic derivatives[18]. The synthetic protocol consists of the mono or multistep, and di-component or multicomponent reactions to get the desired pyranopyrazole moiety. Out of these methods, the Multicomponent reaction is one of the excellent protocols for the preparation of bioactive heterocyclic compounds. The reaction proceeds via all the reactants are mixed together to give the final product, without purification of intermediates compounds. The principle of MCRs, is highly productive, simple protocol, low cost, low wastages, reducing reaction times, and no byproduct.26, the multicomponent is the better reaction as compared with traditional methods. Along with the MCRs are eco friendly, and usually performed by excellent chemoselectivity [19–22]. Recently, various techniques, protocols are available for the efficient preparation of PY derivatives by using multicomponent reactions. The DPy is usually prepared from the MCR of using NH_2-NH_2-H_2O, ethyl acetoacetate, $CH_2(CN)_2$, and aromatic aldehydes by using catalyst-free [23], using acid catalyst [24], using base catalyst [25], using organ catalyst [26], using inorganic catalyst [27], using DTP/SiO_2 [28] catalyst that includes.

We are always interested in the development of novel bioactive heterocyclic[29-35], herein we have reported the synthesis of Simple, Highly efficient synthesis of 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives using silica-supported dodeca-tungstophosphoric acid DTP/SiO_2.

Experimental

All the apparatus and chemicals were used as per standard laboratory guidelines. The M.P. of the novel compound has been done with melting point apparatus thermal IA9100 (Bibby Scientific Limited, Staffordshire, UK). The FTIR of the compound was recorded over the Bruker FTIR instruments. The ^{1}HNMR, ^{13}CNMR recorded over the Bruker-300MHz, Bruker-400 MHz instruments.

Synthesis of 2-amino-4-phenyl-4,5,6,7-tetrahydropyrano[3,2-c]carbazole-3-carbonitrile derivatives (4A).

A mixture of 1,2,3,9-tetrahydro-4H-carbazol-4-one (1mol), aldehyde (2A–2J) (1.1 mol), malononitrile 3 (1.1 mmol), and DTP/SiO_2 (25 wt %) in DMF (10 mL) was stirred at room temp about 30-60 Minute (Table 1). The progress of reaction was checked by TLC. After completing the conversion of reactant into product (by TLC), the catalyst was filtered off To this reaction mixture, ice cold water (40 mL) was added and stirred mechanically for 10-15 min. The solid was separated out, filtered and recrystallized from ethanol to afford the pure products **4 A-4H.**

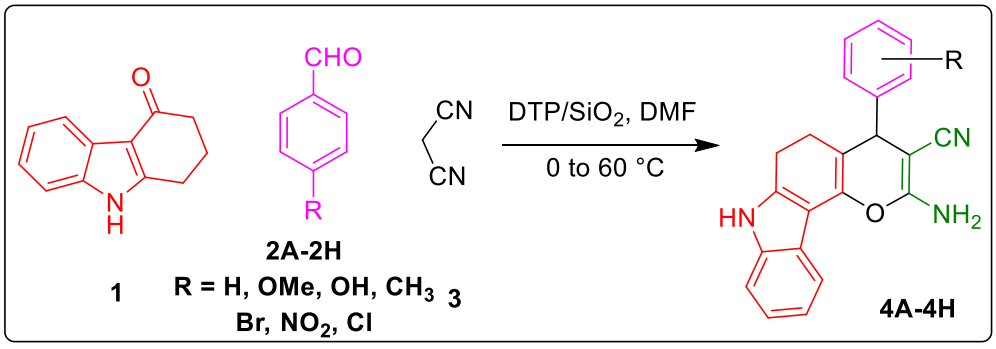
(4A). MP: 244-246 °C; ^{1}H NMR (300 MHz, DMSOd*6*): δ 11.54 (s, 1H), 8.56 (d, 1H, *J*=7.4 Hz,), 7.42 (d, 1H, *J*=8.2), 7.40 (*t*, 1H, *J*=8.2 Hz), 7.35 (*t*, 1H), 7.28-7.16 (m, 5H), 6.80 (s, 2H), 4.87 (s, 1H), 2.54 (m, 2H), 2.34 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d*6*): 160.1, 149.2, 142.3, 136.1, 135.2, 128.4, 127.7, 126.2, 126.2, 125.6, 122.1, 121.7, 119.8, 119.1, 117.2, 111.2, 111.1, 56.4, 43.2, 29.2, 24.7. LCMS (ESI+) calcd. for $C_{22}H_{17}N_3O$339.13; found 340.01 $(M+H)^+$

2-amino-4-(4-chlorophenyl)-4,5,6,7-tetra hydropyrano[3,2-c]carbazole-3-carbonitrile (4F).

MP: 253-260 °C; ^{1}H NMR (300 MHz, DMSOd*6*): δ 11.56 (s, 1H), 8.34 (d, 1H, *J*=7.4 Hz,), 7.12 (d, 1H, *J*=8.1), 7.20 (*t*, 1H, *J*=8.3 Hz), 7.10 (*t*, 1H), 7.05-7.21 (m, 5H), 6.82 (s, 2H), 3.92 (s, 1H), 2.32 (m, 2H), 2.45 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d*6*): 160.1, 149.0, 141.2, 135.6, 135.1, 131.2, 130.4, 128.3, 126.1, 121.6, 119., 119.2, 117.1, 111.0, 111.1, 56.1, 42.4, 29.1, 24.5 LCMS (ESI+) calcd. for $C_{22}H_{16}ClN_3O$ (M+H)+: 373.09; found 374.0

Results and Discussion

The synthesis of carbazole-3-carbonitrile derivatives was achieved by reacting substituted aromatic benzaldehydes **(2a)** with malononitrile **(3)** and 1,2,3,9-tetrahydro-4H-carbazol-4-one **(1)**in DMF solvent in the presence of DTP/SiO_2 as a catalyst. The product was obtained after stirring the reaction mixture for 60 minutes at room temperature. carbazole-3-carbonitrile derivatives **(4a-4H)** were obtained with high purity and better to excellent yields, as shown in **Scheme 1.**



Scheme 1. Synthesis of 6A PyCarbazole carbonitriles

Firstly, we have considered solvent parameters and observed reactions in different solvents like water, methanol, PEG-400, and ethanol as aprotic solvents as well as DCM, DMF, and acetonitrile as aprotic solvents. We observed that the solvent has an important role in the progress of the reaction. The reaction with DMF gave the corresponding product in good yields, whereas the findings with other solvents such as DCM, ethanol, and acetonitrile, yielded the product **4A** in fewer quantities, neither PEG-400 nor water were particularly given good results. Further, it has been decided the impressive and ideal solvent for this conversion was DMF.

The structures of all the newly synthesized **2A**PyCarbazole carbonitriles derivatives (**4A-4J**) are depicted in **Table 1.**

Table 1. Comparison of catalytic activity of various catalysts for synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives

Sr/No	Solvent	Catalyst	Reaction time	Yield
	Water	DTP/SiO_2	120	45
	Methanol	DTP/SiO_2	120	50
	Ethanol	DTP/SiO_2	120	65
	PEG-400	DTP/SiO_2	120	65
	DCM	DTP/SiO_2	120	50
	DMF	DTP/SiO_2	60	82
	CH_3CN	DTP/SiO_2	120	65

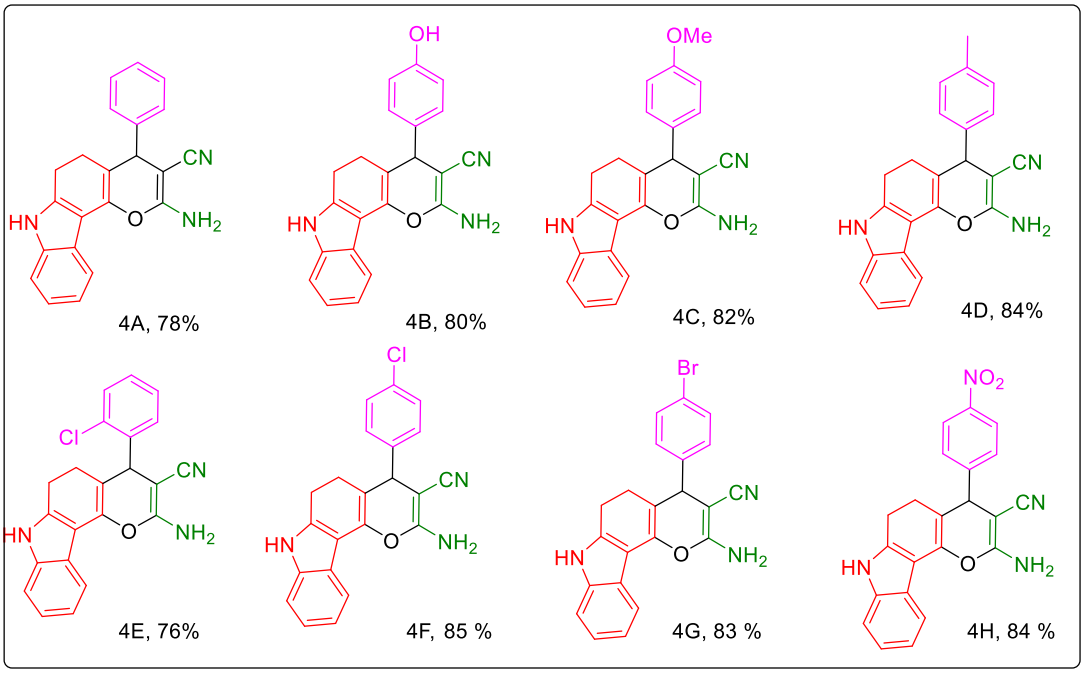
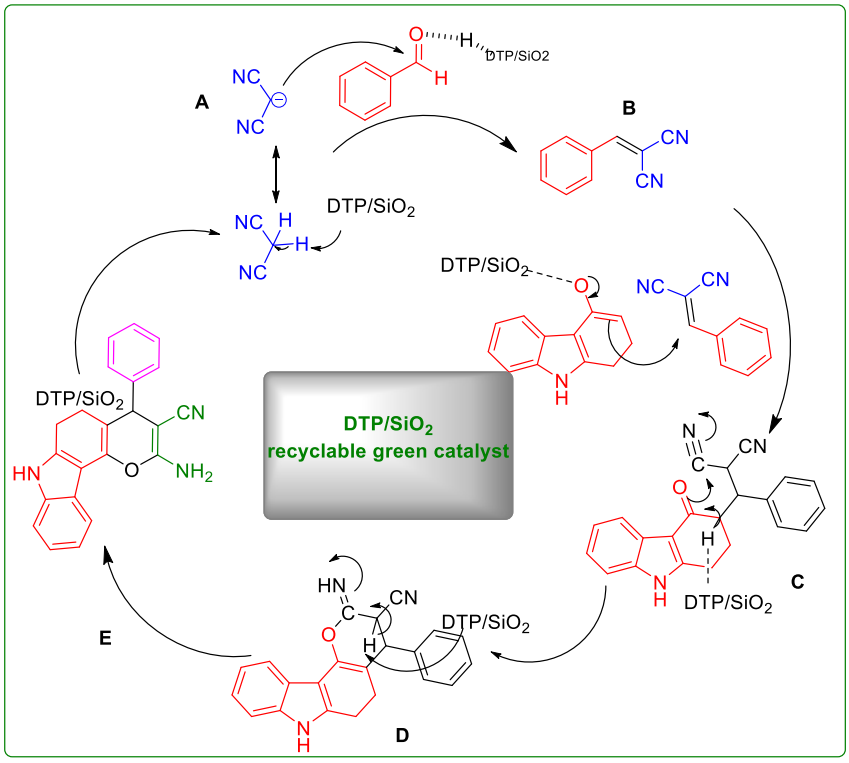


Table 2.DTP/SiO_2 catalyzed synthesis of 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3 -carbonitrile.



Scheme 2. Plausible mechanism for the2-Amino-4-Phenyl-4,5,6,7-Tetrahydropyrano[3,2-c]Carbazole-3-Carbonitrile

However, in the model reaction, the influence of catalyst loading was also investigated. The results revealed that a catalyst concentration of 10 mol% was a great choice for this process. Increasing the catalyst concentration 10 to 15mol% resulted in a low effect on yield and not be further increased. When the reaction was conducted with reducing amounts of catalyst, the yield of **4A** could not be further increased. Under optimized conditions the optimized protocol was carried out in the absence of DTP/SiO_2 there was less conversion of reactants to products after stirring at room temperature.

This result motivates us to investigate the methods for synthesis of carbazole-3-carbonitrile derivatives from substituted benzaldehydes, malononitrile, and 1,2,3,9-tetrahydro-4*H*-carbazol-4-one using a 10mol% DTP/SiO_2 catalyst and DMF as a solvent in an optimized reaction condition. After the completion of the reaction, the product was recovered and the catalyst was isolated by filtration. The Isolated catalyst was again used after drying of catalyst. A series of aromatic aldehydes were selected to undergo the condensation in the presence of a DTP/SiO2 catalyst. As shown in Table 1, aromatic aldehydes 2 carryings either electron-donating or electron-withdrawing substituent reacted efficiently and gave excellent yields Table 2, Therefore, the nature of the substituent's attached to the aromatic ring did not show a significant effect in this conversion. The experimental methods include efficient, eco-friendly, convenient, rapid properties and showed the ability to endure a variety of electron releasing and electron-withdrawing functional groups, such as methoxyl, nitro, hydroxyl, and halides.

Mechanism

The plausible mechanism for the synthesis of 2-amino-4-phenyl-4,5,6,7-tetrahydropyrano [3,2-c]carbazole-3-carbonitrile (**4A**) as shown in **Scheme 2**, involves the proton abstraction of the active methylene group of malononitrile by the DTP/SiO_2, the active methylene compounds react with the nuclophic sites of benzaldehyde

simulteniously the resulted compound undergoes dehydration and producce compound **B (Scheme 2)**, The intermidiates B, which attack on the 1,2,3,9-tetrahydro-4H-carbazol-4-one **(1)** and form the **C.** In the presence of DTP/SiO_2, catalyst the intemediate undergoes intramolecular cyclization and isomerization results in desired product E.

Conclusion

Finally, 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives (4a-l)was prepared from DTP/SiO_2catalyst. we designed a mild, rapid, and environmentally sustainable synthesis process for 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives **(4A-4H)** from aromatic benzaldehyde, malononitrile, and1,2,3,9-tetrahydro-4*H*-carbazol-4-one.
Simple reaction conditions, no side reactions, and high yield product formation are all essential features of the technique. For the synthesis of 2-amino-4-phenyl-4,7-dihydropyrano[3,2-c]carbazole-3-carbonitrile derivatives, the current technique is an alternative to traditional methods. The catalyst was retrieved several times without losing catalytic activity, resulting in a cost-effective method.

Acknowledgments

S.V.G is thankful to the principal Dr. D.Y. Patil Arts, Commerce & Science Women's College; Pimpri, Pune-411018 for research support.

Conflict of Interest

We have no conflicts of interest to disclose.

ORCID

S. V. Gaikwad :
https://orcid.org/0000-0003-0754-1945
M. V. B. Unnamatla :
https://orcid.org/0000-0001-7348-3259

Reference

[1] A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, O. Fadeyi, *Org. Biomol. Chem*., **2016**,*14*, 6611-6637. [Crossref], [Google Scholar], [Publisher]
[2] A. Kumar, P. Lohan, D. K. Aneja, G. Kumar Gupta, D. Kaushik, O. Prakah, *Eur J Med Chem*, **2012**, *50*, 81-89. [Crossref], [Google Scholar], [Publisher]
[3] N. M. Saleh, M. G. El-Gazzar, H. M. Aly, R. A. Othman, *Front. Chem*., **2020**, *7*, 917.[Crossref], [Google Scholar], [Publisher]
[4] A. A. Al-Amiery, R. I. Al-Bayati, F. M. Saed, W. B. Ali, A. A. H. Kadhum, A. Bakar Mohamad, *Molecules*, **2012**, *17*(9), 10377-10389.[Crossref], [Google Scholar], [Publisher]
[5] G. M. Reddy, J. R. Garcia, G. V. Zyryanov, G. Sravya, N. B. Reddy, *Bioorganic Chemistry*, **2019**, *82*, 324-331. [Crossref], [Google Scholar], [Publisher]
[6] K. Rehse, J. Kotthaus, L. Khadembashi, *Arch Pharm*, **2009**, *342*(1), 27-33. [Crossref], [Google Scholar], [Publisher]
[7] M. Mantzanidou, E. Pontiki, D. Hadjipavlou-Litina, *Molecules,* **2021**, *26*, 3439.[Crossref], [Google Scholar], [Publisher]
[8] M. Mantzanidou, E. Pontiki, D. Hadjipavlou-Litina, . *Molecules,* **2021**, *26*, 3439.[Crossref], [Google Scholar], [Publisher]
[9] R. D. Kamble, R. J. Meshram, S. V. Hese, R. A. More, S. S. Kamble, R. N. Gacche, B. S. Dawane, *Computational Biology and Chemistry*, **2016**, *61*, 86-96. [Crossref], [Google Scholar], [Publisher].
[10] D. Matiadis, M. Sagnou, *Int. J. Mol. Sci*., **2020**, *21*(15), 5507. [Crossref], [Google Scholar], [Publisher]
[11] M. Amir, H. Kumar, S. A. Khan, *Bioorganic & Medicinal Chemistry Letters*, **2008**, *18*(3), 918-922. [Crossref], [Google Scholar], [Publisher]
[12] F. M. Abdelrazek, P. Metz, N. H. Metwally, S. F. El-Mahrouky, *Arch Pharm,* **2006**, *339*(8), 456-60. [Crossref], [Google Scholar], [Publisher]
[13] H. E. Temel, M. D. Al tintop, A. Ozdemir, *Biochem. Biophys .Res. Commun.*, **2017**, *22*, 482(4), 615-624. [Crossref], [Google Scholar], [Publisher]
[14] H. A. Allam, A. A. Kamel, M. El-Daly, R. F. George, *Future Med Chem.,* **2020**,*12*(1), 37-50. [Crossref], [Google Scholar], [Publisher]
[15] B. S. Dawane, S. G. Konda, R. G. Bodade, R. B. Bhosale, *Journal of Heterocyclic Chemistry*, **2010**,*47*, 237-241. [Crossref], [Google Scholar], [Publisher]

[16] R. D. Kamble, R. J. Meshram, S. V. Hese, R. A. More, S. S. Kamble, R. N. Gacche, B. S. Dawane, *Computational biology and chemistry*, **2016**, *61*, 86-96.[Crossref], [Google Scholar], [Publisher]
[17] C. Han-Song, L. Zheng-Ming, *Chinese Chemical letter,* **2000**, *18*, 596-602. [Crossref], [Google Scholar], [Publisher]
[18] G. M. Reddy, J. R. Garcia, V. H. Reddy, A. K. Kumari, G. V. Zyryanov, G. Yuvaraja, *Journal of Saudi Chemical Society* , **2019**, *23*, 263-273. [Crossref], [Google Scholar], [Publisher]
[19] S. N. Maddila, S. Maddila, W. E. van Zyl, S. B. Jonnalagadda, *Current Organic Synthesis*, **2016**, 13(6), 89- 900. [Crossref], [Google Scholar], [Publisher].
[20] M. Koohshari, M. Dabiri, P. Salehi, ***RSC Adv.***, **2014**, *4*, 10669-10671. [Crossref], [Google Scholar], [Publisher]
[21] R. K. Ganta, N. Kerru, S. Maddila, S. B. Jonnalagadda, *Molecules*, **2021**, *26*(11), 3270. [Crossref], [Google Scholar], [Publisher]
[22] M. Mamaghani, R. H. Nia, *Polycyclic aromatic compounds*, **2021**, *41*, 223-291. [Crossref], [Google Scholar], [Publisher]
[23] M. Keihanfar, B. B. F. Mirjalili, *BMC Chemistry*, **2022**, *16*, 9.[Crossref], [Google Scholar], [Publisher]
[24] M. Farahi, B. Karami, I. Sedighimehr, H. M. Tanuraghaj, *Chinese Chem. Lett.*, **2014**, *25*, 1580. [Crossref], [Google Scholar], [Publisher]
[25] A.S. Waghmare, S. S. Pandit, *J. Saudi. Chem. Soc.*, **2017**, *21*, 286.[Crossref], [Google Scholar], [Publisher]
[26] R. Maity, S. C. Pan, *Org. Biomol. Chem.*, **2017**, *15*, 8032. [Crossref] [Google Scholar], [Publisher].
[27] K. K. Gangu, S. Maddila, S. N. Maddila, S. B. Jonnalagadda, *RSC. Adv*. **2017**, *7*, 423. [Crossref], [Google Scholar], [Publisher]
[28] R. D. Kamble, M.V. Gaikwad, M. R. Tapare, S. V. Hese, S. N. Kadam, A. N. Ambhore, B. S. Dawane, *J. Appl. Organomet. Chem.*, **2021**, *1*(1), 22-28. [Crossref], [Google Scholar], [Publisher].
[29] S.V.Gaikwad, M.V.Gaikwad, P.D.Lokhande, *J. Heterocycl. Chem.*, **2021**, *58*, 1408. [Crossref], [Google Scholar], [Publisher].
[30] S. Gaikwad, D. Kamble, P. D. Lokhande, *Tetrahedron Lett.*, **2018**, *59*, 2387 [Crossref], [Google Scholar], [Publisher].
[31] S. V. Gaikwad, D. N. Nadimetla, M. Al Kobaisi, M. Devkate, R. Joshi, R. G. Shinde, M. V. Gaikwad, M. D. Nikalje, S. V. Bhosale, P. D. Lokhande, *Chemistry Select*, **2019**, *4*, 10054 [Google Scholar], [Publisher]
[32] S. V. Gaikwad, M. V. Gaikwad, P. D. Lokhande, *Eurasian Chemical Communications*, **2020**, *2*, 945. [Crossref], [Google Scholar], [Publisher].
[33] S.V. Gaikwad, M.V. Gaikwad, P.D. Lokhande, *J. Appl. Organomet. Chem.*, **2021**, *1*, 59. [Crossref], [Google Scholar], [Publisher]
[34] M. V. Gaikwad, R. D. Kamble, S. V. Hese, S. N. Kadam, A. N. Ambhore, S. V. Gaikwad, A. P. Acharya, B. S. Dawane, *Chem. Methodol.,* **2021**, *5*(4), 341-347. [Crossref], [Google Scholar], [Publisher].
[35] B. R. Nawghare, S. V. Gaikwad, A. Raheem, P. D. Lokhande, *J. Chil. Chem. Soc.*, **2014**, *59*, 2284 [Crossref], [Google Scholar], [Publisher]