Orbital
The electronic journal of chemistry

the electronic journal of chemistry

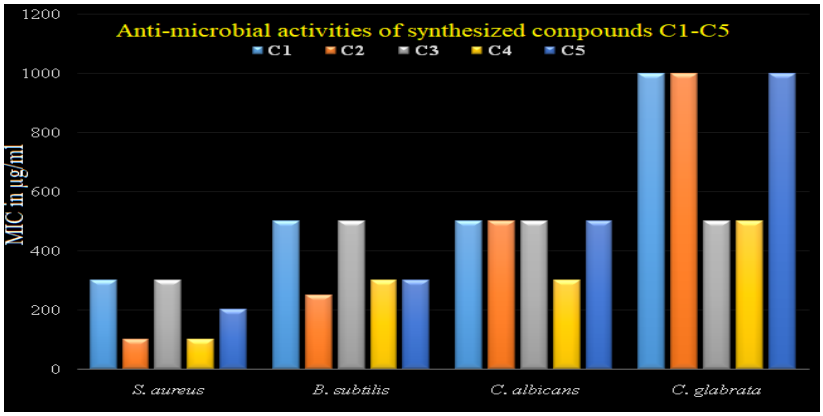
Full Paper | http://dx.doi.org/10.17807/orbital.v15i2.17611

Green Synthesis and Anti-microbial Activities of Some Thiazole-imino Derivatives

Satbir Singh [a,*], Seema Raj [a], Sunil Kumar Sharma [b], Sucheta [c], Vijay Kumar Yadav [a]

The ring forming reaction of furfural imine (A) and substituted acetophenone (B) via a greener approach resulted in the synthesis of thiazole-imino derivatives (C1 – C5). The compound A was synthesized by green method using acetic acid in aqueous media where conc. Sulfuric acid was avoided. The final compounds (C1-C5) were again synthesized in aqueous media avoiding use of organic solvents. The resultant compounds were characterized and distinguished from their precursors by elemental analysis, ^{1}H-NMR, ^{13}C-NMR and IR spectral studies. The in-vitro activities of the final compounds (C1-C5) depicted that they are all appreciably active against bacterial strains *S. aureus*, *B. subtilis* and fungal strains *C. albicans*, *C. glabrata*. Ciprofloxacin and Itraconazole were used as the control drugs for anti-bacterial and for anti-fungal activities; respectively. As compared to the other analogues, compound C2 (R = NO_2) and C4 (R = Cl) showed best activities against the bacterial and fungal strains; respectively.

Graphical abstract



Keywords

Imines
Thiazole
Green synthesis
Anti-microbial activities

Article history

Received 15 Nov 2022
Revised 01 Jun 2023
Accepted 02 Jun 2023
Available online 11 Jul 2023

Handling Editor: Ana C. Micheletti

1. Introduction

Imines (>C=N-) are typically prepared by the condensation of aldehydes or ketones with primary amines [1-3]. They have been of particular interest for a long time in medicinal as well as pharmaceutical applications which can be attributed to their immense biological significance including analgesic, anti-inflammatory, anti-microbial, anti-tubercular, anti-cancer, anti-convulsant, anti-oxidant activities [4-8]. Thiazoles on the other hand, are a part of many biologically active moieties. [9, 10]. Thiazole ring is also present in sulfathiazole (anti-microbial drug) and abafungin (anti-fungal drug). Isoniazid (imino derivative) is another example of a key drug involved in treating tuberculosis [11]. Many such derivatives have found to displayed significant anti-microbial activities [12–16].

Looking at the diversified numerous applications of imines and thiazoles in varied fields of chemistry, there has always been attractive developments pertaining to greener,

[a] School of Basic & Applied Science, K. R. Mangalam University, Gurugram, 122103, Haryana, India. [b] Department of Chemistry, Jaipur National University, Jaipur, 302017, Rajasthan, India. [c] School of Medical & Allied Sciences, K. R. Mangalam University, Gurugram, 122103, Haryana, India. *Corresponding author. E-mail: **singh.rsatbir@gmail.com**

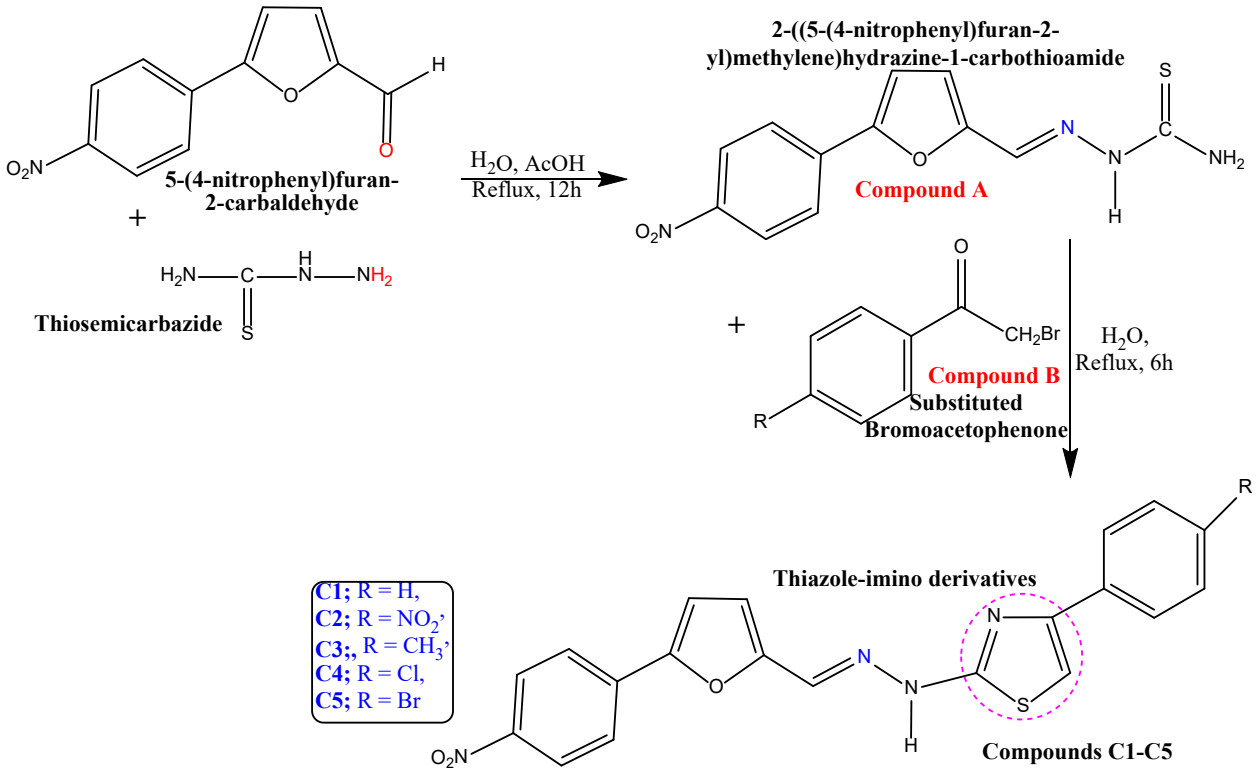
economical, efficient and feasible methods for their synthesis *viz.*, in aqueous media [17, 18]; using catalysts [19-24]; using Microwave Irridiation method [25, 26]. In addition to all these findings; in this research paper, we herein report the green synthesis and anti-microbial evaluation of few thiazole-imino derivatives obtained from furfural imine and substituted acetophenone. These synthesized analogues have showed promising activities against the microbial strains for which they were examined.

2. Material and Methods

The commercially procured chemicals and reagents were used as such without further purification. Carbon, Nitrogen and Hydrogen were analyzed on a Perkin-Elmer C, H, N and S II series 2400 analyzer. IR spectra were recorded using KBr pellet method on a Spectrum Version: 10.4.00 - Perkin Elmer FTIR spectrophotometer in the range 4000-400cm^{-1}. ^{1}H-NMR spectra were recorded for the synthesized compounds using TMS as the internal reference on Bruker Ascend 400 MHz system in DMSO-d_6 (Aquisition Time of about 3 seconds; Software - Mnova). Melting points were determined using Weiss-gallenkamp Electrothermal 9100 apparatus and were uncorrected.

2.1. Green synthesis of Furfural imine

Phenyl substituted furfural (2.63 g, 12.12mmol) and thiosemicarbazide (1.10 g, 12.12mmol) were mixed in water (20 ml) with catalytic amount of acetic acid and the contents were refluxed for about 12 hrs (Scheme 1). The resultant mixture was then cooled to room temperature. The precipitated powdered solid compound (Compound **A**) was filtered, washed twice with cold water and dried.



Scheme 1. Green Synthesis of Thiazole-imino derivatives.

2.2. Synthesis of Thiazole-imino derivatives

Furfural imine (**A**, 0.1mmol) and substituted acetophenone (**B**, 0.1mmol) in water were mixed and refluxed for about 6 hrs (Scheme 1). The resultant mixture was then cooled to room temperature. The precipitated powdered solid compounds (Compounds **C1-C5**) were filtered, washed twice with cold water and dried.

3. Results and Discussion

All the resultant final compounds (**C1-C5**) were synthesized as per the steps shown in Scheme 1. In the first step, compound **A** was prepared via a condensation reaction using Acetic acid and avoiding concentrated Sulfuric acid as reported earlier [27]. In the final step, compounds **A** and **B** interacted to form thiazole ring. The resultant compounds were obtained in 84-93% yield; their Physical and analytical observations are listed in Table 1.

3.1. IR Spectra

IR Spectra of the synthesized analogues (**C1-C5**) were observed in the definite region of 4000-400 cm^{-1}. These spectra were analyzed depending on some key peaks as recorded. The signals in the regions 3300-3185 cm-1 and 3120-3050 cm^{-1} (Table 2) in spectra of derivatives **C1-C5** have been accounted for υ(N−H) and υ(aromatic C−H), respectively. The peaks recorded in the spectra in the region 1600-1580 cm^{-1} (Table 2)are attributed to υ(C=N) of the synthesized analogues which accounts for the imino bond [27-30]. Furthermore, peaks observed in spectra of derivatives in the region 1575-1555 cm^{-1} (Table 2) can be assigned to υ(C=C). The IR Spectrum of a representative compound **C3** is presented as Figure 1.

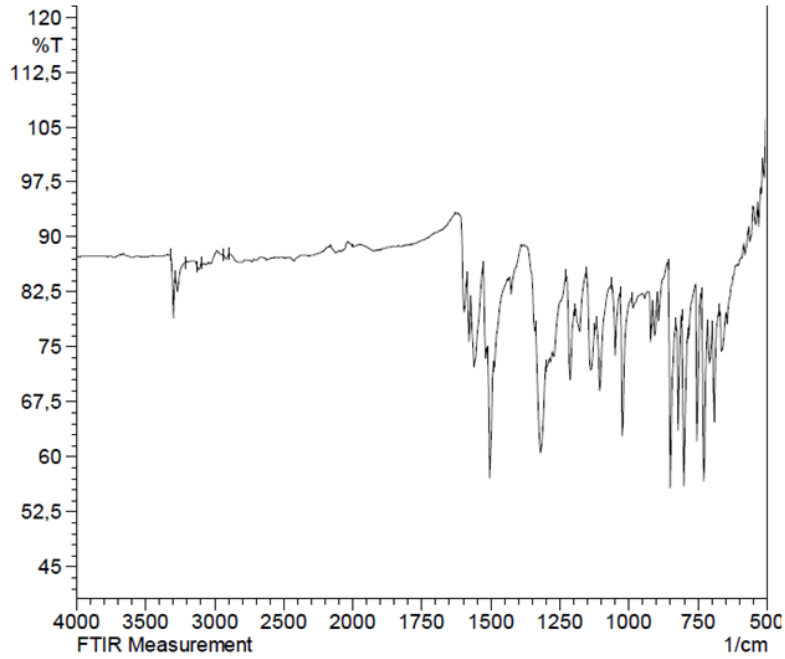


Fig. 1. IR Spectrum of the compound C3.

Table 1. Physical and Analytical data for the synthesized compounds C1-C5.

Compound	Molecular Formula	M.P. (°C)	Yield (%)	Elemental Analysis % Found (% calcd.)		
				C	H	N
C1 (R = H)	$C_{20}H_{14}SN_4O_3S$	212-214	84	61.44 (61.53)	3.51 (3.61)	14.28 (14.35)
C2 (R = NO_2)	$C_{20}H_{13}SN_5O_5$	251-253	90	55.06 (55.17)	3.11 (3.01)	16.17 (16.08)
C3 (R = Me)	$C_{21}H_{16}SN_4O_3$	235-237	92	62.22 (62.36)	3.93 (3.99)	13.66 (13.85)
C4 (R = Cl)	$C_{20}H_{13}ClSN_4O_3$	228-230	87	56.40 (56.54)	2.96 (3.08)	13.06 (13.19)
C5 (R = Br)	$C_{20}H_{13}BrSN_4O_3$	242-244	93	51.16 (51.18)	2.83 (2.79)	11.87 (11.94)

Table 2. IR spectral readings for the synthesized compounds C1-C5.

Compound	υ(N-H)	υ(C-H, aromatic)	υ(C=N)	υ(C=C)
C1 (R = H)	3300	3050	1600	1555
C2 (R = NO_2)	3290	3115	1600	1570
C3 (R = Me)	3275	3110	1580	1560
C4 (R = Cl)	3310, 3190	3120	1590	1565
C5 (R = Br)	3185	3115, 3060	1585	1575

3.2. ^{1}H-NMR Spectra

The presence of broad singlet (br.s.) signals observed in 12.42-12.31 ppm region (Table 3) in the proton spectra of all the synthesized compounds can be attributed to >N-H proton; which clearly implies that this proton has not been compromised during thiazole ring formation [27]. Additionally, signals observed in 8.29-6.95 ppm region (Table 3) are assigned to aromatic protons in the proton spectra of these compounds. The similarity of the shifts of the signs of these derivatives can be seen in Table 3. Peak observed at 2.30 ppm is assigned to the methyl (-CH_3) protons in compound **C3**. The ^{1}H-NMR Spectrum of a representative compound **C3** is presented as Figure 2.

Table 3. ^{1}H-NMR spectral readings for the synthesized compounds C1-C5.

Compound	^{1}H-NMRδ in ppm (400 MHz, DMSO-d_6)
C1 (R = H)	12.33 (br.s., 1H), 8.29-8.26 (m, 2H), 8.01 (s, 1H), 7.98-7.95 (m, 2H), 7.87-7.84 (m, 2H), 7.43-7.39 (m, 3H), 7.36 (s, 1H), 7.32-7.29 (m, 1H), 7.00 (d, 1H)
C2 (R = NO_2)	12.42 (br.s., 1H), 8.29-8.23 (m, 4H), 8.09-8.07 (m, 2H), 7.97-7.94 (m, 3H), 7.73 (s, 1H), 7.42 (d, 1H), 7.01 (d, 1H)
C3 (R = Me)	12.31 (br.s., 1H), 8.27 (d, 2H), 7.95-7.93 (m, 3H), 7.73 (d, 2H), 7.39 (d, 1H), 7.25-7.19 (m, 3H), 6.97 (d, 1H), 2.30 (s, 3H)
C4 (R = Cl)	12.35 (br.s., 1H), 8.26 (d, 2H), 7.96-7.86 (m, 5H), 7.46-7.37 (m, 4H), 6.97 (d, 1H)
C5 (R = Br)	12.34 (br.s., 1H), 8.25-8.23 (m, 2H), 7.95-7.90 (m, 3H), 7.80-7.78 (m, 2H), 7.58-7.56 (m, 2H), 7.39-7.35 (m, 2H),6.95 (d, 1H)

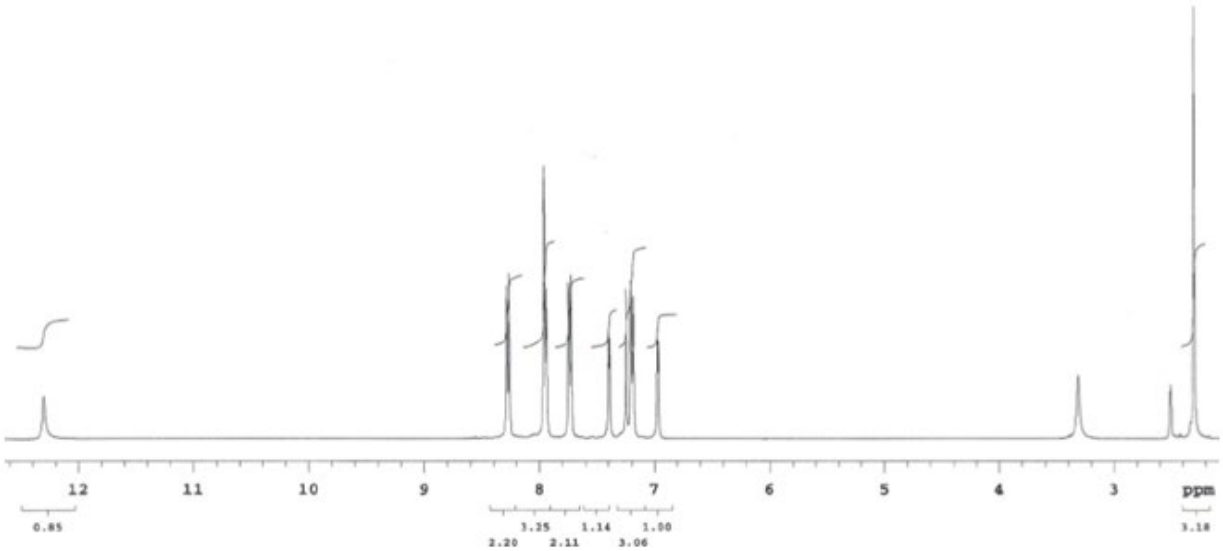


Fig. 2. ^{1}H-NMR Spectrum of the compound C3.

3.3. ^{13}C-NMR Spectra.

The presence of signals observed in 173-170 ppm (Table 4) region in the ^{13}C-NMR spectra of all the synthesized compounds (**C1-C5**) can be attributed to the Carbon of the -N=C-S- ring moiety; which clearly implies thiazole ring formation. Additionally, peak observed at 24 ppm (Table 4) is assigned to the methyl (-CH_3) Carbon in compound **C3**. The ^{13}C-NMR Spectrum of a representative compound **C3** is presented as Figure 3.

Table 4. ^{13}C-NMR spectral readings for the synthesized compounds C1-C5.

Compound	^{13}C-NMR δ in ppm
C1 (R = H)	170.29, 152.63, 149.71, 148.97, 148.23, 133.21, 132.97, 132.12, 130.16, 129.34, 126.17, 124.51, 124.29, 116.27, 111.05, 106.72
C2 (R = NO_2)	172.81, 151.74, 148.93, 147.64, 146.35, 145.98, 144.12, 136.46, 134.31, 129.52,127.37, 125.76, 124.10, 117.37, 110.39, 105.72
C3 (R = Me)	171.36, 153.18, 151.29, 150.39, 148.77, 136.20, 134.16, 133.84, 132.91, 131.27, 128.48, 126.63, 124.71, 115.90, 111.22, 105.37, 24.17
C4 (R = Cl)	170.57, 151.46, 150.23, 148.45, 145.51, 134.48, 133.66, 133.03, 131.76, 129.16,125.42, 124.13, 123.08, 109.56, 107.44, 102.92
C5 (R = Br)	171.16, 151.56, 150.36, 149.23, 146.13, 135.87, 133.64, 131.78, 127.89, 126.43, 125.12, 123.09, 121.59, 111.38, 108.44, 104.67

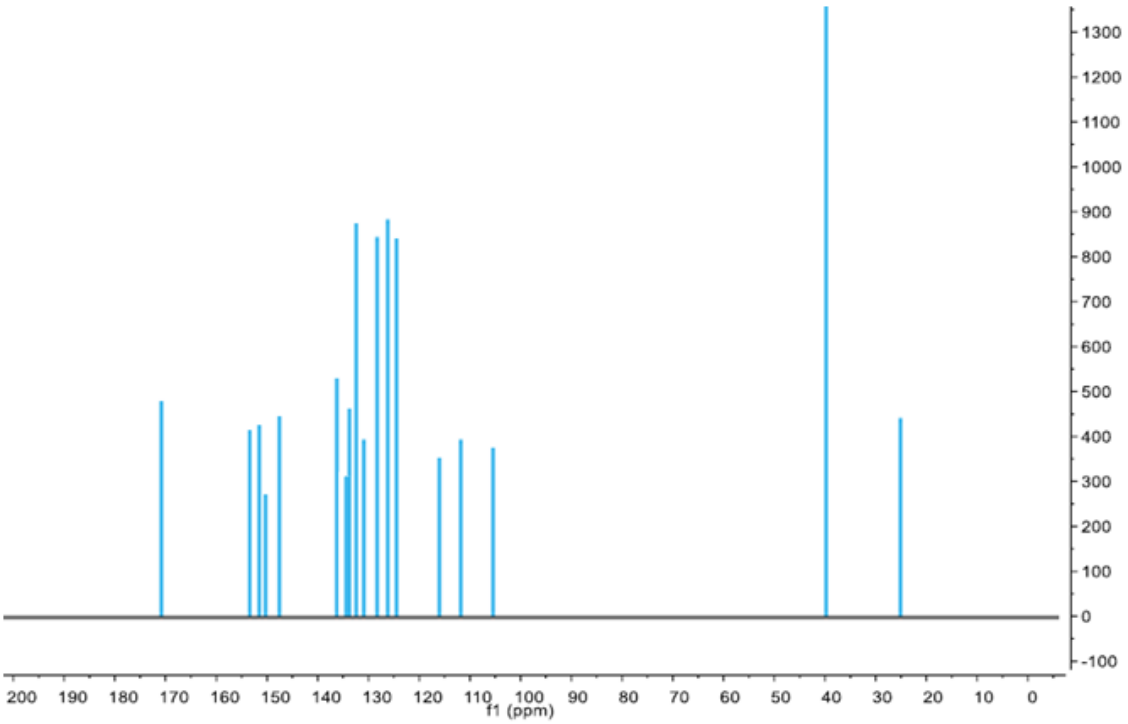


Fig. 3. ^{13}C-NMR Spectrum of the compound C3.

3.4. Anti-microbial Activities

The synthesized analogs were evaluated for their anti-microbial activities against bacterial strains (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6051) and fungal strains (*C. albicans* ATCC 14053 and *C. glabrata* ATCC 15545). For this purpose; Ciprofloxacin was used as the control drug for anti-bacterial activity (Table 5) and Itraconazole for anti-fungal activity using Kirby-Bauer well diffusion method [31, 32]. The strains were swabbed upon Sabouraud's Dextrose Agar as Muller Hinton (MH) Agar medium and plates were incubated for 2 days at 28°C.

Anti-bacterial evaluation of the synthesized thiazole-imino derivatives (**C1-C5**) reveals that they show appreciable activities against both *S. aureus* and *B. subtilis*. Compound **C2** (R = NO_2) showed the best activities against both the bacterial strains compared to the other analogues (Table 5). When tested against the fungal strains; it was observed that analogue **C4** (R = Cl) proved to be better as compared to the other analogues (Table 5). Overall; it was found that the analogues showed better anti-bacterial significance compared to their anti-fungal activities and they are least active towards *C. glabrata*.

Table 5. Anti-microbial activity results for the synthesized compounds C1-C5.

Compound	MIC concentrations (µg/ml)			
	Bacterial Strains		Fungal Strains	
	***S. aureus* ATCC 25923**	***B. subtilis* ATCC 6051**	***C. albicans* ATCC 14053**	***C. glabrata* ATCC 15545**
C1 (R = H)	300	500	500	1000
C2 (R = NO_2)	100	250	500	1000
C3 (R = Me)	300	500	500	500
C4 (R = Cl)	100	300	300	500
C5 (R = Br)	200	300	500	1000
Ciprofloxacin	50	25	---	---
Itraconazole	---	---	5	5

4. Conclusions

In the presented work; green synthesis of some thiazole-imino derivatives obtained from furfural imine and substituted acetophenone; have been reported. The use of Sulfuric acid as well as organic solvents were avoided by carrying out the reactions in aqueous media. All of these synthesized analogues were characterized based on their elemental analysis, ^{1}H-NMR, ^{13}C-NMR and IR spectral studies. The anti-microbial evaluation of these compounds demonstrates their significant biological activities against *S. aureus*, *B. subtilis*, *C. albicans* and *C. glabrata*. As compared to the other analogues, compound **C2** (R = NO_2) and **C4** (R = Cl) showed best activities against the bacterial and fungal strains; respectively. From the futuristic point of view, more such derivatives can be synthesized via Greener approach and they may be able to demonstrate better bio-activities.

Author Contributions

Satbir Singh: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. Seema Raj: Conceived and designed the experiments; Analyzed and interpreted the data. Sunil Kumar Sharma: Conceived and designed the experiments; Analyzed and interpreted the data. Sucheta: Analyzed and interpreted the data. Vijay Kumar Yadav: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

References and Notes

[1] Bigelow, L. A.; Eatough, H. *Organic Syntheses* **1928**, *8*, 22. [Crossref]

[2] Wittig, G.; Hesse, A. *Organic Syntheses* **1970**, *50*, 66. [Crossref]

[3] Chandramouli, C.; Shivanand, M. R.; Nayanbhai, T. B.; Bheemachari, B.; Udupi, R. H. *J. Chem. Pharm. Res.* **2012**, *4*, 1151.

[4] Venkatesh, P. *Asian Journal of Pharmaceutical and Health Sciences* **2011**, *1*, 8.

[5] Sondhi, S. M.; Singh, N.; Kumar, A.; Lozach; O.; Meijer, L. *Bioorg. Med. Chem.* **2006**, *14*, 3758. [Crossref]

[6] Aboul-Fadl, T.; Mohammed, F. A. H.; Hassan, E. A. *Arch. Pharmacal. Res.* **2003**, *26*, 778. [Crossref]

[7] Chinnasamy, R. P.; Sundararajan, R.; Govindaraj, S. *J. Adv. Pharm. Technol. Res.* **2010**, *1*, 342. [Crossref]

[8] Murray, J. H.; Harding, M. M. *J. Med. Chem.* **1994**, *37*, 1936. [Crossref]

[9] Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles, 2nd Ed.; Wiley-VCH: Weinheim, Germany,* 2003, 149. [Crossref]

[10] Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry Volume II: Five-Membered Heterocycles; Springer: Berlin, Germany,* 1999, 416. [Crossref]

[11] Judge, V.; Narasimhan, B.; Ahuja, M. *Med. Chem. Res.* **2012**, *21*, 3940. [Crossref]

[12] Sah, P. P. T.; Peoples, S. A. *J. Am. Pharm. Assoc.* **1954**, *43*, 513. [Crossref]

[13] Chakravarty, D.; Bose, A.; Bose, S. *J. Pharm. Sci.* **1964**, *53*, 1036. [Crossref]

[14] Gürsoy, A.; Terzioglu, N.; Ötük, G. *Eur. J. Med. Chem.* **1997**, *32*, 753. [Crossref]

[15] Vicini, P.; Zani, F.; Cozzini, P.; Doytchinova, I. *Eur. J. Med. Chem.* **2002**, *37*, 553. [Crossref]

[16] Kumar, P.; Narasimhan, B.; Sharma, D.; Judge, V.; Narang, R. *Eur. J. Med. Chem.* **2009**, *44*, 1853. [Crossref]

[17] Sharma, D.; Nag, P. *Res. J. Pharm. Technol.* **2022**, *1*, 24. [Crossref]

[18] Illán, J. A. M.; Miguel, D. R. S.; Franco, C.; Imaz, I.; Maspoch, D.; Luis, J. P.; Zamora, F. *Chem. Commun.* **2020,** *56*, 6704**.** [Crossref]

[19] Adams, M. R.; Tien, C. H.; Huchenski, B. S. N.; Ferguson, M. J.; Speed A. W. H. *Angew. Chem., Int. Ed.* **2017**, *56*, 1. [Crossref]

[20] Yadav, G.; Mani, J. V. *Int. J. Sci. Res.* **2015**, *4*, 121.

[21] Reeves, J. T.; Visco, M. D.; Marsini, M. A.; Grinberg, N.; Busacca, C. A.; Mattson, A. E.; Senanayake, C. H. *Org. Lett.* **2015**, *17*, 2442. [Crossref]

[22] Lv, X.; Zhou, Y.; Zhang, A.; Zhou, L.; Zeng, Q. *Toxicol. Environ. Chem.* **2015**, *98*, 1155. [Crossref]

[23] Patil, R. D.; Adimurthy, S. *Asian J. Org. Chem.* **2013**, *2*, 726. [Crossref]

[24] Xu, J.; Zhuang, R.; Bao, L.; Tang, G.; Zhao, Y. *Green Chem.* **2012**, *14*, 2384. [Crossref]

[25] Singh, G. S. *Asian J. Org. Chem.* **2022**, *21*, e202100803.

[26] Mohammed, S. J.; Sheat, A. M.; Abood, S. A.; Yahya, O. M. *Egypt. J. Chem.* **2021**, *64*, 6423.

[27] Holla, B. S.; Malini, K. V.; Rao, B. S.; Sarojini, B. K.; Kumari, N. S. *Eur. J. Med. Chem.* **2003**, *38*, 313. [Crossref]

[28] Nag, P.; Sharma, D. *Rev. Roum. Chim.* **2021**, *64*, 331.

[29] Sharma, D.; Nag, P. *Orbital: Electron. J. Chem.* **2021**, *1*, 48. [Link]

[30] Zuo, Z.; Liu, J.; Nan, J.; Fan, L.; Sun, W.; Wang, Y.; Luan, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 15385. [Crossref]

[31] Patel, A. B. *J. Chem. Res.* **2020**, *44*, 315. [Crossref]

[32] Brown, D. F. J.; Kothari, D. *J. Clin. Pathol. (London)* **1975**, *28*, 779. [Crossref]

How to cite this article

Singh, S.; Raj, S.; Sharma, S. K.; Sucheta.; Yadav, V. K. A. *Orbital: Electron. J. Chem.* **2023**, *15*, 76. DOI: http://dx.doi.org/10.17807/orbital.v15i2.17611