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Synthesis and Spectral Analysis of Heterocyclic Compounds Derived from Chalcone Derivatives

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ABSTRACT

In this research, we conducted the synthesis of derivatives **(2a-c)** derived from 4-fluoro-3-methylacetophenone (FMAP) **(1)** using aldol condensation with substituteddibromobenzaldehydes **(a-c)**. The condensation process occurred in ethanol with the presence of a base, leading to the creation of chalcone derivatives **(2a-c)**. These chalcones serve as crucial intermediates for the production of a diverse array of heterocyclic products. Upon reaction with hydrazine, pyrazol derivatives **(3a-c)** were obtained, while the use of hydroxylamine hydrochloride resulted in the formation of isoxazole **(4a-c)**. Additionally, the reaction with urea produced oxazine derivatives **(5a-c)**. We characterized all these compounds using spectral techniques, monitoring their reactions through TLC and measuring melting points. Subsequently, we assessed the biological activity of these compounds against two distinct bacterial strains.

Keywords: Chalcone, Isoxzazole, Biological activity, Antifungal activities.

INTRODUCTION

Chalcones, a subset of the flavonoid class, hold considerable significance in the field of medicine due to their diverse range of applications. Within the broader category of flavonoids, chalcones play pivotal roles in medicine and are particularly renowned for their multifaceted biological effects. These effects encompass a spectrum of advantages, including but not limited to biological properties[1-4].

Pyrazoles, a crucial category of heterocyclic compounds, stand out with their distinctive five-member ring structure featuring two adjacent

nitrogen atoms. The pharmacological impact of pyrazole derivatives is noteworthy, showcasing a variety of biological activities[5-7]. The unique structural arrangement of pyrazoles contributes significantly to their potential therapeutic applications.

Isoxazole derivatives, well-recognized for their importance in medicine, exhibit a broad spectrum of biological activities, rendering them valuable compounds. These activities include analgesic, anticancer, antibiotic, anti-inflammatory, antioxidant, antibacterial, and antifungal properties[8-11]. The versatility of isoxazole derivatives underscores their potential across diverse medical applications, emphasizing their profound significance in the field of pharmacology.

EXPERIMENTAL

MATERIALS AND METHODS

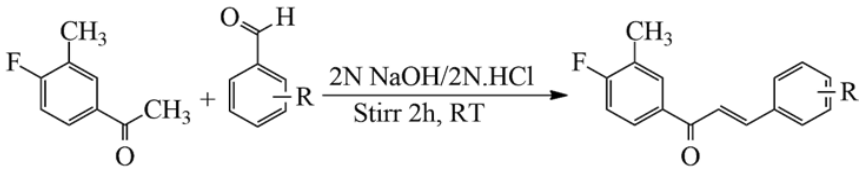
For this investigation, we sourced AR-grade chemicals from reputable suppliers. These materials underwent meticulous industry-standard drying or purification processes, ensuring their quality and appropriateness for experimental use. The melting points of the synthetic compounds, without any modifications, were measured using open capillary tubes, serving as a foundational measure for their thermal properties.

To assess the progression of reactions and the conversion of products, we employed thin-layer chromatography (TLC). Silica gel was used as the stationary phase, while petroleum ether and ethyl acetate acted as the mobile phases, enabling the compounds to move through the chromatographic process. This method was crucial in confirming the successful progress of reactions and the creation of the desired products.

The structural analysis phase involved the utilization of advanced instrumentation, This included using a Brucker FT-IR spectrometer for infrared spectra and a Brucker 400 MHz spectrometer for nuclear magnetic resonance (NMR) spectra. These advanced instruments were crucial in obtaining detailed information about the molecular composition and structure of the synthesized compounds, offering valuable information about their chemical characteristics. The scrupulous application of these methodologies underscores our dedication to precision and rigor in the experimental procedures undertaken in this study.

Chalcone Synthesis General Method

Within a solution composed of 50 mL of ethanol, a meticulous process unfolded wherein 0.01 mol of FMAP (1) and diverse benzaldehyde derivatives (2,3-dibromobenzaldehyde, 3,4-dibromobenzaldehyde, 2,5-dibromobenzaldehyde) were dissolved. The amalgamation underwent vigorous stirring for 30 min, after which 10 mL of a 2N NaOH solution was carefully added, drop by drop. Following this, the resulting concoction was permitted to stand undisturbed for an extended period of 8 h before undergoing a precise neutralization process with 2N HCl, inducing the precipitation of the intended compounds.



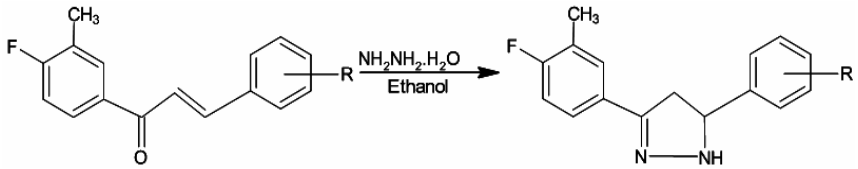
Scheme 1. Chalcone (2a-c) Synthesis General Method

Pyrazole Derivatives (3a-c) Synthesis

In the ethanol medium, a carefully measured quantity of chalcone (2a-c) amounting to 0.001 mol was combined with 0.5 ml of hydrazine hydrate within a 25 mL volume. This resulting mixture underwent a reflux process, where it was allowed to boil gently for an extended period of 3 hours. Following this reflux period, the reaction mixture was subjected to a cooling process, and the subsequent product was separated through filtration. The separated material underwent thorough drying before proceeding to a refinement stage, wherein it was meticulously recrystallized using ethanol as the solvent. This methodological sequence, as referenced in[12],

emphasizes the precision and attention to detail in ensuring the successful synthesis and purification of pyrazole derivatives.

The resulting precipitate, carefully obtained from the reaction, underwent a subsequent phase of air-drying and was then subjected to a meticulous recrystallization process utilizing ethanol as the solvent, following the detailed procedures outlined in reference[12]. This systematic approach ensures the precision and reproducibility of the synthesis, laying the foundation for obtaining high-quality and well-characterized chalcone derivatives.

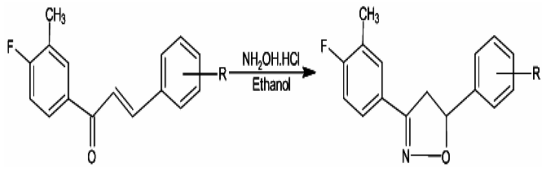


Scheme 2. Synthesis of 3a-c

Synthesis of Isoxazole Derivatives (3a-c)

To initiate the synthesis process, a mixture of Chalcone (2a-c) (0.001 mol), hydroxylamine hydrochloride (0.005 mol), and 0.5 mL of 2N aqueous sodium hydroxide was carefully dissolved in 30 mL of ethanol. The resulting solution was subjected to an extensive reflux process, lasting for 5-6 hours. Following the refluxing phase, the solution underwent a controlled transition into ice-cold water, a strategic step that facilitated the subsequent filtration process. The filtered residue obtained was subjected to a meticulous washing procedure and subsequently underwent a precisely executed recrystallization technique utilizing ethanol as the solvent.

This stringent recrystallization process, as outlined in reference[13], yielded a set of refined isoxazole derivatives (4a-c). The deliberate use of standardized methodologies underscores the commitment to achieving reproducibility and purity in the synthesis of these compounds, ensuring their suitability for further analyses and applications in various scientific contexts.

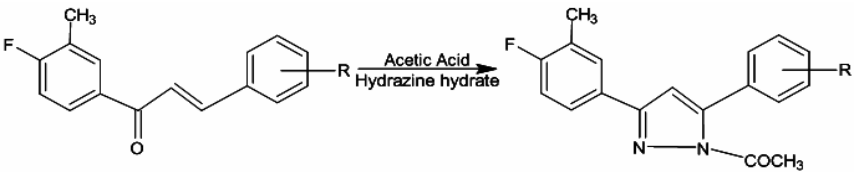


Scheme 3: Synthesis of 4a-c

Synthesis of Acyl Derivatives (5a-c)

To begin the synthetic process, a solution was carefully prepared by dissolving 0.001 mol of chalcone and 0.002 mol of hydrazine hydrate in 5 mL of glacial acetic acid. This resulting solution underwent a prolonged period of agitation, spanning 12 h, to ensure comprehensive reaction and interaction between the components. The solution was then gradually added to 50 mL of cold water, with continuous stirring for 30 minutes. The resultant mixture, indicative of the evolving chemical transformation, was left undisturbed throughout the night, allowing for the formation and settling of the anticipated solid product.

The following day, the solid product was subjected to a meticulous filtration to separate it from the residual liquid components. The separated solid underwent a thorough washing procedure to eliminate impurities and any remnants of the reaction mixture. To further refine and enhance the purity of the synthesized compound, the solid underwent a controlled recrystallization process, employing ethanol as the solvent. This elaborate series of steps, detailed in reference[14], emphasizes the systematic approach and attention to detail employed to ensure the successful synthesis and purification of acyl derivatives (5a-c).



Scheme 4. Acylated derivatives (5a-c) Synthesis

Preparation of Microbiology Culture Media

To prepare the culture media, dissolve 28 g of nutrient agar in 1 liter of distilled water, followed by sterilization in an autoclave at 121°C for 15 minutes. Once sterilized, the media was carefully poured into Petri dishes and allowed to cool to 37°C to facilitate bacterial streaking. The study included *Staphylococcus aureus* and *Escherichia coli*, both hospital-isolated pathogens, enhancing the investigation's comprehensiveness. For the evaluation of various compounds, solutions were prepared with dimethylformamide (DMF) as a solvent, using a concentration of 0.02 g of compound per 5 mL of DMF. The inhibitory zones of all compounds were assessed as described in reference[15]. Bacterial cultures were incubated at 37°C for 24 h, allowing for thorough observation of the compounds' effects on bacterial growth, thereby providing insights into their potential antimicrobial properties.

RESULTS AND DISCUSSION

FT (IR) Spectra

The infrared spectra of compounds 2a-c showed clear bands in particular regions, each serving as an indicator of unique molecular features. Noteworthy is the segment between 1590-1659 cm^{-1}, which disclosed stretching vibrations corresponding to the (C=O) functionality within the chalcone group. The stretching vibrations of aromatic hydrogen (Ar-H) were observed between 3042 and 3098 cm^{-1}, and the stretching vibrations of the bromo group (C-Br) appeared in the 624-686 cm^{-1} range. Within the range of 2919-2956 cm^{-1}, stretching vibrations of the methine group (-CH=) were identified. Additionally, the methyl group's (CH_3) stretching vibrations (C-H) were observed between 2921-3058 cm^{-1}. The infrared spectra also indicated aromatic (C=C) stretching vibrations between 1581 and 1610 cm^{-1}, as well as aliphatic (C=C) stretching vibrations ranging from 1445 to 1497 cm^{-1}.

In the context of compounds (3a-c), their infrared spectra showcased characteristic bands within well-defined regions, offering valuable insights into their molecular composition. In the infrared spectra, a band between 1639 and 1723 cm^{-1} indicated the presence of a (C=N) pyrazol group, while another band in the range of 2923-3085 cm^{-1} indicated an (Ar-H) group. Within the same region of 2923-3085 cm^{-1}, a band indicated the presence of an (N-H) group in imidazole, which overlapped with the band for (N-H) pyrazoles at 3390-3395 cm^{-1}. Bands in the range of 631-688 cm^{-1} indicated the presence of a (C-Br) group. Distinct bands at 2923-3065 cm^{-1} and 2851-2925 cm^{-1} corresponded to (C-H) groups in (CH_3) and (-CH=), respectively. Notably, a band at 1441-1578 cm^{-1} suggested the presence of aromatic (C=C) bonds.

Moving to the infrared spectra of compounds (4a-c), specific bands emerged within defined regions, offering insights into their key molecular characteristics. Bands between 1584 and 1666 cm^{-1} indicated the presence of the (C=N) isoxazoles functional group, while bands in the range of 2971-3076 cm^{-1} indicated (Ar-H) aromatic hydrogen groups. Bands at 2887-2924 cm^{-1} were indicative of the (-CH_2-) group, and the (C-Br) group was highlighted by bands at 674-682 cm^{-1}. Additionally, bands at 3070-3243 cm^{-1} pointed to (C-H) groups in the (CH_3) methyl group. Further insights were provided by bands at 1409-1439 cm^{-1}, indications of (N=N) groups were suggested by bands, while bands between 1419 and 1591 cm^{-1} showed evidence of aromatic (C=C) bonds. Notably, bands at 1316-1393 cm^{-1} pointed to the presence of (C-O) bonds within the isoxazole ring.

The infrared (IR) spectrum of compounds (5a–c) revealed unique bands suggesting the presence of –C=N and carbonyl C=O groups. Specifically, bands were observed around 1581–1605 cm^{-1} and 1661–1725 cm^{-1}, corresponding to these functional groups. Additionally, the IR spectra of compounds (4a–c) showed distinct bands around 3065–3068 cm^{-1}, associated with C–H sp^3 stretching in the –$COCH_3$ group. It is noteworthy that a band at 640-686 cm^{-1} in the IR spectra of acylated pyrazoles (5a-i) indicated the stretching of C-F bonds in the aromatic ring.

Table 1: FTIR spectra of the prepared chalcone derivatives (cm^{-1})

Compound	Ar C-H	-CH_3	N-H	-CH=	Ar-C=C	Ali-C=C	C=O	C=N	C-Br
2a	3098	-	-	2956	1571	1497	1590	-	686
2b	3055	-	-	2919	1556	1471	1586	-	663
2c	3042	-	-	2922	1610	1445	1559	-	624
3a	-	-	2923	-	1592	1483	-	1660	683
3b	3065	-	2923	2856	-	1581	-	1675	692
3c	3068	2968	2947	2913	-	1581	-	1661	677
4a	3085	3065	-	2850	1501	-	-	1723	688
4b	3088	2923	-	2852	1501	-	-	1661	656
4c	3051	2923	-	2851	1557	-	-	1667	666
5a	3177	3018	-	2887	1553	-	1591	1666	682
5b	3243	3076	-	2853	1556	-	1583	1713	674
5c	3070	2971	-	2954	1552	-	1584	1672	674

^{1}H NMR Spectra

The ^{1}H NMR spectra of compounds (2a-c) show chemical shifts (δ) ranging from 7.16 to 7.93 (multiplet, 7H, aromatic protons), 2.35-2.38 (singlet, 3H, methyl group), 7.06-7.16 (singlet, 1H, vinyl group), and 7.35 (doublet, 1H, aldehyde group). These measurements were conducted using dimethyl sulfoxide (DMSO) as the solvent. Regarding compounds (3a-c), their 1H NMR analysis in DMSO displayed values of 7.02-7.98 (multiplet, 7H, Ar-H), 1.28-2.32 (singlet, 3H, CH_3), 2.56-3.51 (doublet, 2H, CH2 pyrazole ring), 4.99-5.02 (triplet, 1H, CH pyrazole ring), and 7.02-7.07 (singlet, 1H, NH imidazole ring).

The ^{1}H NMR spectra of compounds (4a-c) in DMSO revealed shifts of 6.89-7.79 (multiplet, 7H, Ar-H), 1.59-2.38 (singlet, 3H, CH_3), and 6.79-6.89 (doublet, 1H, O-CH isoxazole ring).

The confirmation of the structures of compounds (5a-c) was confirmed by analyzing their ^{1}H NMR spectra. In the ^{1}H NMR patterns of compounds 5a–c, a distinctive singlet corresponding to the acyl group $COCH_3$ protons was observed at δ 2.33–2.36 ppm. The singlet readings in the high-field region (δ 2.41–4.46 ppm), totaling three protons, were identified as -CH_3 protons. Notably, compounds 4a-c displayed a pair of doublet-of-doublet resonances at δ 3.10-3.16 ppm (J = 7.33-8.00 Hz, J = 11.29-11.68 Hz) and δ3.77-3.85 ppm (J = 4.21-4.22 Hz, J = 7.09-11.37 Hz) corresponding to the CH_2 protons of the pyrazoline ring. Additionally, Hx-7 manifested as a doublet-of-doublet at δ 5.62-5.64 (J = 0.55–0.56 Hz, J = 8.03–8.11 Hz). In the aromatic region ranging from 7.04-7.55 ppm, multiplets representing five or six protons were discerned, providing further insights into the molecular composition of these compounds.

Table 2: ^{1}H NMR spectra of the prepared chalcone derivatives (ppm)

Compound	-CH_3	$COCH_3$	N-H	Ar-C-H	-CH=	Ar-CH_2-	Ar-CH	O-CH
2a	2.351	-	-	7.137-7.925	7.943	-	-	-
2b	2.396	-	-	6.938-7.902	7.943	-	-	-
2c	2.371	-	-	7.110-7.928	7.936	-	-	-
3a	2.359	-	7.072	7.101-7.615	-	3.091	5.518	-
3b	2.331	-	7.036	6.917-7.638	-	3.720	5.622	-
3c	2.356	-	7.061	7.299-7.660	-	3.102	5.616	-
4a	2.350	-	-	7.300-7.636	-	3.723	5.588	-
4b	2.357	-	-	7.077-7.599	-	3.105	5.508	-
4c	2.328	-	-	7.023-8.081	-	3.296	5.920	-
5a	2.343	2.467	-	7.071-7.616	-	3.847	5.930	6.989
5b	2.300	2.447	-	7.073-7618	-	3.810	5.858	7.015
5c	2.345	2.468	-	7.199-7.624	-	3.850	5.787	7.043

CONCLUSION

The main objective of this ongoing research endeavor was to embark on the synthesis and characterization of innovative fluorinated chalcones along with their derivatives. This scientific inquiry initiated by transforming the initial compound, namely substituted benzaldehydes, into a diverse array of target compounds. The primary focus lies in unraveling the unique properties and potential applications of these newly synthesized fluorinated chalcones and their derivatives through a comprehensive synthesis and characterization process.

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Conflict of interest

The authors affirm that there are no conflicts of interest.

REFERENCES

1. Goyal, K.; Kaur, R.;Goyal, A.;Awasthi,R., *J. Applied Pharm. Science*., **2021**, *11*(1), 1-14.
2. Mukhtar, S. S.; Saleh, F. M.; Hassaneen, H. M.; Hafez, T. S.; Hassan, A. S.; Morsy, N. M. M.; Teleb, A. M., *Synthetic Communications.,* **2022**, *52*(19-20), 1909-1916.
3. Kucerova-Chlupacova, M.; Vyskovska-Tyllova, V.; Richterova-Finkova, L.; Kunes, J.; Buchta,V.; Vejsova,M.; Opletalova, V., *Molecules*., **2016**, *21*(11), 1421.
4. Dhaliwal, J. S.; Moshawih, S.; Goh, K. W.; Loy, M. J.; Hossain, M. S.; Hermansyah, A.; Ming, L. C., *Molecules*., **2022**, *27*(20), 7062.
5. Faisal, M.; Saeed, A.; Hussain, S.; Dar, P.; Larik, F. A., *Journal of Chemical Sciences*., **2019**, *131*, 1-30.
6. Chen, M.; Zhang, X.; Lu, D.; Luo, H.; Zhou, Z.; Qin, X.; Zhang, G., *Frontiers in Chemistry*., **2021**, *9*, 645876.
7. Shehry, M. F.El.; Ghorab, M. M.; Abbas, S. Y.; Fayed, E. A.; Shedid, S. A.; Ammar, Y. A., *European Journal of Medicinal Chemistry*., **2018**, *143*, 1463-1473.
8. Kulkarni, P., *Journal of the Indian Chemical Society*., **2021**, *98*(1), 100013.
9. Abd-Al-Hussain, H. A. A.; Aljamali, D. N. M., *International Journal of Pharmaceutical Research*., **2021**, *13*(1).
10. Khan, A. K., *Al-Mustansiriyah Journal of Science*., **2017**, *28*(3), 122-133.
11. Lokeshwari, D. M.; Kumar, K. A., *Asian Journal of Chemistry*., **2017**, *29*(12), 2660-2664.
12. Khidre, R. E.; ElƟGogary, S. R.; Mostafa, M. S., *Journal of Heterocyclic Chemistry*., **2017**, *54*(4), 2511-2519.
13. Tomma.; J. H. Khazaal.; M. S. Baker.; R. KIbn *AL-Haitham Journal For Pure and Applied Science*., **2017**, *30*(3), 68-76.
14. Majed, A. A.; Abid, D. S., *Annals of the Romanian Society for Cell Biology*., **2021**, 11935-11945.
15. Kumar, A.; Gupta, V.; Singh, S.; Gupta, Y. K., *Research Journal of Pharmacy and Technology*., **2017**, *10*(4), 1155-1159.