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Synthesis of New Hydrazones Containing 1,3-Diketo Moiety

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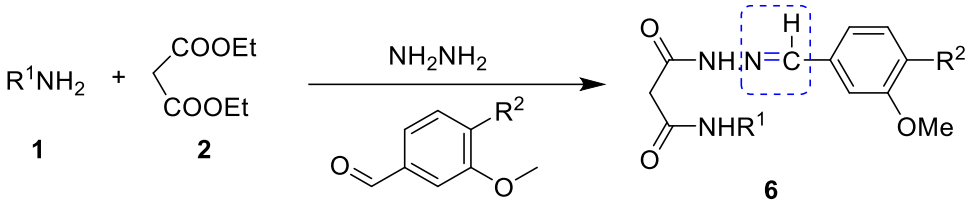

Abstract: A series of novel hydrazones containing a 1,3-diketo moiety, namely 3-[(2*E*)-2-(4-hydroxybenzylidene)hydrazino]-3-oxo-N-phenylpropanamides (**6a-j**), were synthesized as precursors for biologically important β-lactam and thiazolidinone derivatives. The synthesis involved the condensation of 3-methoxy-4-hydroxybenzaldehyde or 3-methoxy-4-acetyloxybenzaldehyde with various substituted malonanilic acid hydrazides. The hydrazides (**4a-e**) were prepared by refluxing aniline with diethyl malonate, followed by treatment with hydrazine hydrate. The structures of the synthesized compounds were confirmed by elemental analysis and spectroscopic techniques, including IR, and ^{1}H NMR spectrometry. The purity of the compounds was ascertained by thin-layer chromatography. The synthesized hydrazones (**6a-j**) were obtained in good yields (62-83%) and were soluble in dimethylformamide. The present study provides a foundation for further exploration of these 1,3-diketo amino compounds as promising scaffolds for developing novel heterocyclic compounds with diverse biological activities.

***Keywords**: 1,3-diketo amino compounds, hydrazones, antimicrobials, azetidinone, β-lactam, synthesis, thiazolidinone.*

INTRODUCTION

Hydrazones are versatile intermediates in organic synthesis, crucial in developing various chemical compounds, including pharmaceuticals, agrochemicals, and functional materials. The synthesis of new hydrazones containing a 1,3-diketo moiety has an emerging interest due to the diverse biological activities and potential pharmaceutical applications of these compounds (Halve et al., 2008). Hydrazones, characterized by the azomethine group (−NHN=CH), are synthesized through the reaction of hydrazides with aldehydes or ketones, often resulting in compounds with notable pharmacological properties such as antibacterial, anticancer, and anti-inflammatory activities (Halve et al., 2005).

Their extensive synthetic applications range from serving as precursors for complex molecules to facilitating specific chemical transformations. One significant application of hydrazones is in the synthesis of biologically active compounds. For instance, novel indole-based hydrazone derivatives were prepared and evaluated for their antitubercular and anticancer activities, demonstrating the potential of hydrazones in medicinal chemistry (Cihan-Üstündağ et al., 2015). Similarly, the synthesis of hydrazone derivatives from 5-nitro-furan and 5-iodo-vanillin has been reported, highlighting their potential as anti-inflammatory agents (Reddy, 2017). These examples underscore the importance of hydrazones in developing therapeutic agents.

Hydrazones are also pivotal in various chemical transformations. For example, they can undergo reactions such as the Bamford-Stevens and the Shapiro reactions, essential for synthesizing diazo compounds and other nitrogen-containing derivatives (Fang et al., 2020). Fang et al. described a $PhI(OAc)_2$-promoted 1,2-diaza-Cope rearrangement of β,γ-unsaturated hydrazones, which provides access to diacyl and acyl N-allyl hydrazines, showcasing their utility in synthesizing complex structures (Fang et al., 2020). Moreover, the palladium-catalyzed C(sp^2)-H alkylation of aldehyde-derived hydrazones with functionalized difluoromethyl bromides has been established, allowing for the generation of difluoroalkylated products, which are valuable in various applications (Prieto et al., 2015).

The use of hydrazones as intermediates in asymmetrical synthesis is another notable application. The transition metal-catalyzed asymmetrical hydrogenation of hydrazones has emerged as a direct method for producing chiral hydrazines, which are essential in pharmaceuticals (Li et al., 2021). For instance, nickel-catalyzed asymmetrical hydrogenation has been reported, further emphasizing the role of hydrazones in generating optically active compounds (Li et al., 2021). Additionally, using chiral boranes for enantioselective hydrogenation of hydrazones has yielded high enantiomeric excess, reinforcing their significance in asymmetrical synthesis (Yu et al., 2023).

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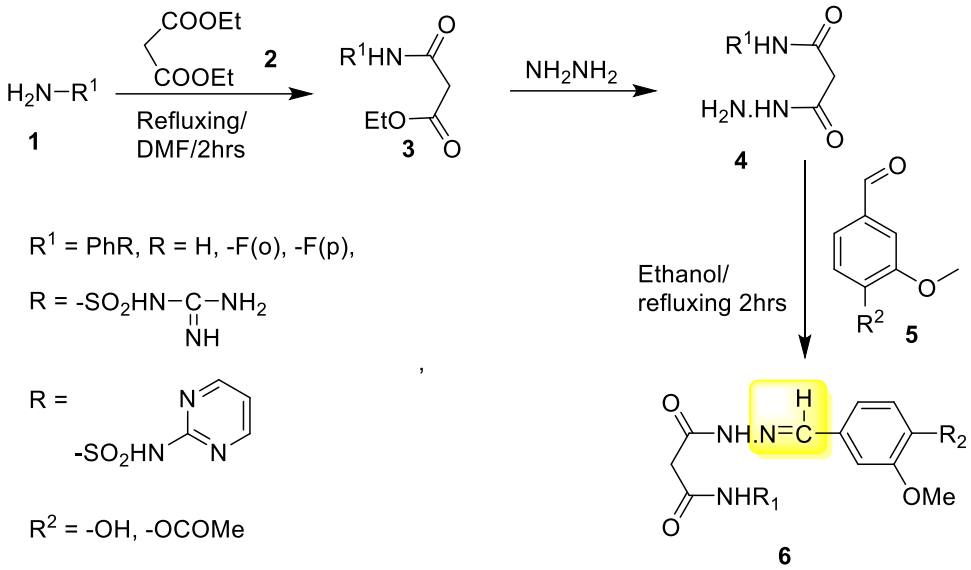
Furthermore, hydrazones can serve as precursors for various functional groups through oxidative transformations. Monge et al. demonstrated the transformation of hydrazones into β-nitronitriles, which are valuable intermediates for synthesizing β-amino acids (Monge et al., 2013). This highlights the potential of hydrazones in generating valuable building blocks for further synthetic applications.

Their ability to participate in various chemical transformations and serve as precursors for biologically active compounds underscores their importance in academic and industrial research. Here, we report the synthesis of 1,3-diketo-containing hydrazones. These molecules are good starting points for β-lactams (Kaur et al., 2018; Kaur et al., 2020; Kaur et al., 2020), thiazolidinones, and many other heterocycles. Considering these facts, a study was designed to prepare 1,3-diketo compounds having azomethine linkage (**Scheme 1**).



Scheme 1. *Synthesis of 1,3-diketo moiety containing hydrazones*

RESULTS AND DISCUSSION

The primary aim of this study was to synthesize novel hydrazones containing a 1,3-diketo moiety. To start with the synthetic strategy depicted in Scheme 1, hydrazones (**6a-j**) were prepared from (**4a-e**) using modified literature methods. (Rathore & Ittyerah, 1960) The present investigation records the reaction of 3-methoxy,4-hydroxybenzaldehyde (**5a**) and 3-methoxy,4-acetyloxy benzaldehyde (**5b**) with five substituted malonanilic acid hydrazides (**4a-e**) and 10 new substituted hydrazones (**6a-j**), is formed in a yield ranging from 62 to 83%. Other hydrazones were prepared by condensing sulfadiazine, sulfa guanidine, *o*-fluoro, *p*-fluoro-substituted malonanilic acid hydrazide with 3-methoxy, 4-hydroxy benzaldehyde (**5a**), and 3-methoxy, 4-acetyloxy benzaldehyde (**5b**). Table 1 presents the yields, melting points, and solubility of the synthesized hydrazides (**4a-e**).

Table 1: Physical Data of Hydrazides

Compound nos.	R^1	MP °C	Color	Yield (%)	Mol. Formula
4a	H	125–127	creamy white	60	$C_9H_{11}O_2N_3$
4b	F(o)	150–152	creamy white	60	$C_9H_{10}O_2\ N_3F$
4c	F(p)	140–142	creamy white	62	$C_9H_{10}\ O_2N_3F$
4d	sulfadiazine	110–112	creamy white	55	$C_{13}H_{14}O_4N_6S$
4e	sulfaguanidine	120–122	creamy white	50	$C_{10}H_{14}O_4N_6S$

The synthesized hydrazones (**6a-j**) were obtained in good yields ranging from 62% to 83%. The IR spectra of the compounds showed characteristic absorption bands for the 1,3-diketo moiety. A positive correlation was observed between the electron-donating groups on the benzaldehyde and the yield of the hydrazones. A significant increase in yield was noted when the reaction time was extended from 4 hours to 6 hours. The substitution pattern on the aniline ring significantly affect the solubility of the hydrazones in dimethylformamide. During the synthesis process, it was observed that the hydrazones were obtained in good yields and were soluble in dimethylformamide. The synthesized compounds were confirmed through various spectroscopic techniques, ensuring their structural integrity and purity. The IR, and ^{1}H NMR data collectively supported the successful synthesis and structural confirmation of the hydrazones. Future studies will focus on the synthesis of β-lactam and thiazolidinone derivatives from these hydrazones to evaluate their biological activities.

The choice of starting materials and the condensation process were crucial in achieving the desired structural features of the hydrazones, which are essential for their biological activity. The successful synthesis and characterization of these hydrazones

suggest their viability as intermediates in the production of β-lactam and thiazolidinone derivatives. While the initial results are promising, further in-depth biological studies are necessary to fully understand the potential and limitations of these compounds.

EXPERIMENTAL (MATERIALS AND METHODS)

Chemicals and Materials

All chemicals and solvents used in the synthesis were purchased from Merck, Spectrochemzon, and/or SD Fine-Chem. The melting points were determined by open capillary using the digital melting point apparatus and were not corrected.

Characterization Methods

IR spectra were scanned on a PerkinElmer RXI (FTIR) spectrophotometer, and ^{1}H NMR spectra on a Bruker (Newark, DE, United States) DRX 300 (300 MHz, FT NMR) in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. The chemical shift values are expressed as parts per million downfield from the TMS, and the J values are expressed in hertz (Hz). Split patterns are indicated as s singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, and br: broad peak. Thin layer chromatography was used to monitor the reaction using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm) and an iodine chamber.

METHODS OF SYNTHESIS

General procedures for the synthesis of 4-formyl-2-methoxyphenyl acetate (5b).

4-hydroxy-3-methoxy benzaldehyde (**5a**, 5.32 g, 0.35 M) was dissolved in aqueous NaOH solution (25 ml; 2.5 N), and crushed ice (50 g) was added along with acetic anhydride 5.7 ml. The contents were stirred vigorously for 1 hr. The resulting solid was filtered and successively washed with NaOH solution (0.1 N; 20 ml). The product was recrystallized from petroleum ether (60–80 °C) as white shining crystals. The purity of the compounds was determined by TLC using 2:3 acetone and on silica gel-G plates, and the spots were visualized using iodine vapors. The resulting compound was white solid: Yield; 4.0 g (60%), MP: 64 °C. (KBr): 1690 (sharp, C=O (aldehydic), 1757 (sharp, C=O acetyloxy), 1279.8 and 1032.9 (sharp, OMe, two bands) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 9.6 (s, 1H), 7.3-7.6 (m, 3H, ArH), 3.92 (*s*, 3H, OCH_3), 2.35 (*s*, 3H, $COCH_3$)

General procedure for the synthesis of 3-hydrazinyl-3-oxo-N-phenylpropanamide (4a).

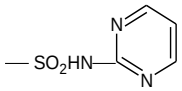
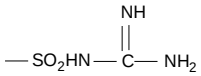
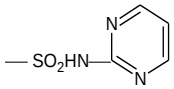
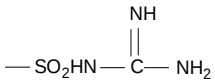
A mixture of aniline (5 ml), diethyl malonate (12 ml), and dimethyl formamide (2 drops) was refluxed for 30 min in a round bottom flask having an air condenser (18 cm) in such a way that the alcohol formed escaped and diethyl malonate flowed back into the flask. The contents were cooled, ethanol was added, and the dianilide was filtered when separated out. The filtration was concentrated to about a third volume. Hydrazine hydrate (80%, 3 ml) was added to it and left overnight. Acid hydrazide was filtered and recrystallized from aqueous ethanol. The purity of the compounds has been ascertained by TLC using n-hexane and 9: 1: 10 chloroform-methanol and n-hexane mixture on silica gel-G plates, and spots were visualized using iodine vapors. Yield; 2.9 g, 60% (Lit. 67%) (Rathore & Ittyerah, 1960), creamish white solid; MP; 180–182 °C (Lit 186 °C) (Rathore & Ittyerah, 1960); IR (KBR): C = O (1,3-diketo) (str.) 1660.14, C = N (azomethine str.)1621, ArC-H (str.) 3012, N-H (diketo amino str.), 3,065.55, cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 10.03 (bs, 1H, CONHPh), 9.3 (bs, 1H, CONHNH_2), 7.3-7.5(m, 5H, ArH), 5.1 (NH_2). 3.1(s, 2H).Other hydrazides (**Table 1**) were prepared by a similar method in the range of 50–62%, having a sharp melting point and soluble in DMF.

General procedure for the synthesis of *E*-3-(2-(4-hydroxy-3-methoxybenzylidene) hydrazinyl)-3-oxo-N-phenylpropanamide (6a-j).

3-methoxy,4-hydroxybenzaldehyde (**5a**, 0.760 g, 0.005 mol) was dissolved in ethanol, 5 ml, and a solution of 3-hydrazinyl-3-oxo-N-phenylpropanamide (**4a**, 0.965 g, 0.005 M) in ethanol, 5 ml was added. The mixture was refluxed for 3 hr and left overnight in an ice bath. When the acid hydrazone separated, it was collected and further purified by recrystallization from ethanol, yielding reddish-brown shining crystals of hydrazones. The recrystallized 1,3-diketoamino analogs (hydrazones, **6a**) are colored, have a sharp melting point, are soluble in DMF, and recrystallized using 1:1 aqueous ethanol. The purity of the compounds was determined by TLC (2:3 acetone and n-hexane and 9:1 chloroform and methanol mixture) on silica gel-G plates, and the spots were recrystallized using iodine vapors. Spectral studies have confirmed structure.

The aforementioned procedure prepared other hydrazones (**6b-j**) (Table 2) by condensing o-fluoro, p-fluoro, sulfadiazine, sulfaguanidine, substituted malonanilic acid hydrazide with 3-methoxy,4-hydroxybenzaldehyde **5a**, and 3-methoxy,4-acetyloxybenzaldehyde **5b**, respectively. All 1,3 diketo amino analogs prepared were colored, yielding 62–83%, and were soluble in DMF.

Table 2 Physical Data of Hydrazones

Compound nos.	R^1 = PhR R	R^2	Color	MP °C	Yield (%)	Mol. Formula
6a	H	OH	DO	191–192	65	$C_{17}H_{17}N_3O_4$
6b	F(o)	OH	Y	172–173	75	$C_{17}H_{16}N_3O_4F$
6c	F(p)	OH	Y	180–181	65	$C_{17}H_{16}N_3O_4F$
6d		OH	CB	145–146	83	$C_{21}H_2ON_6O_6S$
6e		OH	LB	160–162	62	$C_{18}H_2ON_6O_6S$
6f	H	OCOMe	CW	230–232	70	$C_{19}H_{19}N_3O_5$
6g	F(o)	OCOMe	CB	192–194.	62	$C_{19}H_{18}N_3O_5F$
6h	F(p)	OCOMe	Y	185–186	74	$C_{19}H_{18}N_3O_5F$
6i		OCOMe	O	130–131	77	$C_{23}H_{22}N_6O_7S$
6j		OCOMe	Y	170–172	80	$C_{20}H_{22}N_6O_7S$

Abbreviations: CW: cream white, LB: light brown. DO: Dark Orange, Y: Yellow, CB:Chocolate Brown, LB: Light Brown, CW: Cream White, O: Orange

E-3-(2- [4-hydroxy-3-methoxybenzylidene] hydrazinyl) −3-oxo-N-phenylpropanamide (6a).

Yield 65%. Mp 190–192 °C. Dark orange solid. IR (KBr) $\bar{\nu}$ 3,432 (OH), 3,285 (NH), 1660 (C = O), 1592 (C = N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H, NH_a), 8.10 (s, 1H, CH=N), 7.90 (s, 1H, NH_β), 7.58 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.12–6.82 (m, 3H), 3.72 (s, 3H, OCH_3), 3.38 (s, 2H, CH_2).

E-N-(2-fluorophenyl)-3-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)-3-oxopropanamide (6b)

Yield 75%. Mp 172–174 °C. Yellow solid. IR (KBr) $\bar{\nu}$ 3,435 (OH), 3,280 (NH), 1664 (C = O), 1590 (C = N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H, NH_a), 8.40 (s, 1H, CH=N), 8.00 (s, 1H, NH_β), 7.96 (dd, J = 8.0, 1.6 Hz, 1H), 7.42 (td, J = 7.8, 1.6 Hz, 1H), 7.24–7.15 (m, 2H), 7.10–7.00 (m, 3H), 3.70 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2).

E-N-(4-fluorophenyl)-3-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)-3-oxopropanamide (6c).

Yield 65%. Mp 180–182 °C. Yellow solid. IR (KBr) $\bar{\nu}$ 3,435 (OH), 3,282 (NH), 1664 (C = O), 1592 (C = N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H, NH_a), 7.40 (s, 1H, NH_β), 7.40 (s, 1H, CH=N), 7.54 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 8.8 Hz, 2H), 7.15–7.00 (m, 3H), 3.68 (s, 3H, OCH_3), 3.39 (s, 2H, CH_2).

E-3-(2-(4-hydroxy-3-methoxybenzylidene) hydrazinyl)-3-oxo-N-(4-[N-(pyrimidin-2-yl)sulfamoyl] phenyl) propanamide (6d).

Yield 83%. Mp 145–147 °C. Chocolate brown solid. IR (KBr) $\bar{\nu}$ 3,432 (OH), 3,285 (NH), 1664 (C = O), 1620 (C = N), 1,130 (SO_2) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H, NH_a), 7.60 (s, 1H, NH_β), 7.40 (s, 1H, CH=N), 7.82 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.50–7.00 (m, 3H), 3.72 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2).

E-N-(4-(N-carbamimidoylsulfamoyl)phenyl)-3-(2-(4-hydroxy-3-methoxybenzylidene) hydrazinyl)- 3-oxopropanamide (6e).

Yield 62%. Mp 160–162 °C. Light brown solid. IR (KBr) $\bar{\nu}$ 3,432 (OH), 3,285 (NH), 1667 (C = O), 1624 (C = N), 1,132 (SO_2) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H, NH_a), 7.60 (s, 1H, NH_β), 7.40 (s, 1H, CH=N), 7.78 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.50–7.00 (m, 3H), 3.72 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2).

E-2-methoxy-4-([2-(3-oxo-3-(phenylamino) propanoyl) hydrazono] methyl) phenyl acetate (6f).

Yield 70%. Mp 230–232 °C. Creamish white solid. IR (KBr) $\bar{\nu}$ 3,285 (NH), 1757 (C = O acetyloxy), 1664 (C = O), 1620 (C = N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H, NH_β), 9.90 (s, 1H, NH_a), 8.47 (s, 1H, CH=N), 7.60–7.58 (m, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.15–7.05 (m, 2H), 3.70 (s, 3H, OCH_3), 3.47 (s, 2H, CH_2), 2.83 (s, 3H, $OCOCH_3$).

E-4-((2-(3-((2-fluorophenyl)amino)-3-oxopropanoyl)hydrazono)methyl)-2-methoxyphenyl acetate (6g).

Yield 62%. Mp 190–192 °C. Chocolate brown solid. IR (KBr) $\bar{\nu}$ 3,282 (NH), 1750 (C = O acetyloxy), 1667 (C = O), 1622 (C = N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H, NH_a), 7.60 (s, 1H, NH_β), 7.40 (s, 1H, CH=N), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.42 (td, J = 7.8, 1.6 Hz, 1H), 7.50–7.00 (m, 5H), 3.68 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2), 2.80 (s, 3H, $OCOCH_3$).

E-4-([2-(3-[(4-fluorophenyl) amino]-3-oxopropanoyl) hydrazono] methyl)-2-methoxyphenyl acetate (6h).

Yield 74%. Mp 185–187 °C. Yellow solid. IR (KBr) $\bar{\nu}$ 3,285 (NH), 1757 (C = O acetyloxy), 1665 (C = O), 1620 (C = N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H, NH_a), 7.60 (s, 1H, NH_β), 7.40 (s, 1H, CH=N), 7.58 (dd, J = 8.8, 5.2 Hz, 2H), 7.18 (t, J = 8.8 Hz, 2H), 7.50–7.00 (m, 3H), 3.68 (s, 3H, OCH_3), 3.39 (s, 2H, CH_2), 2.83 (s, 3H, $OCOCH_3$).

E-2-methoxy-4-([2-(3-oxo-3-[(4-[N-(pyrimidin-2-yl) sulfamoyl] phenyl) amino] propanoyl) hydrazono] methyl) phenyl acetate (6i).

Yield 77%. Mp 130–132 °C. Orange solid. IR (KBr) $\bar{\nu}$ 3,285 (NH), 1757 (C = O acetyloxy), 1665 (C = O), 1620 (C = N), 1,124 (SO_2) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H, NH_a), 9.60 (s, 1H, NH_β), 8.40 (s, 1H, CH=N), 8.00–7.14 (m, 7H), 3.72 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2), 2.82 (s, 3H, $OCOCH_3$).

E-4-([2-(3-[(4-[N-carbamimidoyl sulfamoyl] phenyl) amino]-3-oxopropanoyl) hydrazono] methyl)-2-methoxyphenyl acetate (6j).

Yield 80%. Mp 170–172 °C. Yellow solid. IR (KBr) $\bar{\nu}$ 3,282 (NH), 1750 (C = O acetyloxy), 1667 (C = O), 1622 (C = N), 1,120 (SO_2) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H, NH_a), 7.60 (s, 1H, NH_β), 7.40 (s, 1H, CH=N), 7.82 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.50–7.00 (m, 3H), 3.72 (s, 3H, OCH_3), 3.40 (s, 2H, CH_2), 2.88 (s, 3H, $OCOCH_3$).

CONCLUSION

In conclusion, the successful synthesis of novel hydrazones containing a 1,3-diketo moiety has been achieved in good yields ranging from 62% to 83%., and their structures were confirmed through comprehensive spectroscopic analyses. This study provides a foundational framework for the synthesis of novel hydrazones that can be further explored for developing new heterocyclic compounds with significant biological activities. The synthesized hydrazones hold potential for application in the pharmaceutical industry, particularly in the development of new antimicrobial, antifungal, anticonvulsant, antitumor, and antitubercular agents. The novelty of this research lies in the successful synthesis of a new series of hydrazones containing a 1,3-diketo moiety, which has not been extensively explored before.

FUTURE SCOPE

Future research should focus on the biological evaluation of these hydrazones and their derivatives to fully explore their potential as antimicrobial, antifungal, anticonvulsant, antitumor, and antitubercular agents. It is speculated that modifying the substituents on the hydrazones could further enhance their biological activity and scope of application.

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