Research Article
Facile and straightforward synthesis of Hydrazone derivatives

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This study was undertaken to report the swift, facile and convenient synthesis of novel hydrazones obtained by condensation reaction between 2-Amino-3-formylchromone and hydrazine derivatives. Various characterization techniques such as MALDI Mass, FTIR, 1HNMR and 13CNMR spectrum analysis was done to determine the chemical structure of these novel six hydrazones. Furthermore, UV-Vis and fluorescence spectra was studied to calculate $\lambda_{\text{max}}$ and $\varepsilon_{\text{max}}$. These hydrazones are quite useful for their facile synthesis and chemical structure. Such hydrazones require separate clinical research to find their applications in biomedical fields.

1. Introduction

Hydrazones are special organic compounds derived from the Schiff-base family and comprising of $\text{C} \equiv \text{N} \equiv \text{N} \equiv \text{C} \equiv \text{N}$ bonds with additional donor sites. The donor sites make hydrazones more flexible and versatile for their structural and functional properties [1]. For instance, hydrazones are very significant reactants in different reactions such as hydrazone iodination, Shapiro and Bamford-Stevens reaction. On the other hand, hydrazones act as intermediates in Wolff-Kishner reaction. The C and H atoms in hydrazones tend to react with organometallic nucleophiles. Due to its highly acidic nature, the alpha-hydrogen atom of hydrazones is comparatively more nucleophilic than that of ketones [2]. Different studies have reported the biological importance of trigonal hybridized nitrogen atom in azomethine group of hydrazones which is remarkable for having one pair of electrons in its either $\pi$ or sp$^2$ orbitals [3, 4]. Their heteroatomic nature and specific electronic properties make them very important structural compounds [5]. One of the most promising organic hole transporting materials are aromatic hydrazones. Recently, some researchers have reported the synthesis of polymeric hydrazones with remarkable properties such as high glass transition temperatures, good filmformation and moderate charge transport [6].

The ligation of hydrazones with surface immobilized hydrazines and aldehydes-modified antibodies can be used to anchor captured proteins on oxide coated biosensor substrates [7]. Hydrazones are also being used as inhibitors such as strong poly (ADP-ribose) glycohydrolase (PARG) [8].
Aroyl hydrazones have been reported to use in clinical theranostic applications due to their ferric ion scavenging activities [9]. The role of N, O and S in metal coordination at the active sites of numerous metalloenzymes is also well known for various industrial, antimicrobial, anticancer and herbicidal applications [10, 11]. The chelating ligands are coordinated with metal ions by N, O or S as donor atoms. They have been found to show a wide variety of biological applications and are becoming a hotspot of research [12, 13]. The coordination of metal ions with the biologically active compounds can enhance their potential [14]. The polymeric hydrazones and their coordination in polymer drug conjugates is involved in hydrolysis. The rate of hydrolysis is significantly faster at acidic pH as compared to those of carbamates [15]. Hydrazone linkers are stable only in physiological conditions (pH 7.4) but they are prone to get cleaved under acidic conditions such as the intracellular conditions of endosomes and lysosomes protects them by forming micelle around. The hydrophobic drugs are hence gets protected from the host defense system in the body [16]. For instance, the anticancer drug DOX is released at higher rate under acidic conditions due to the nature of linkage between the DOX and micelles [17]. Chromone derivatives have received great attention of researchers for their applications. These compounds show wide spectrum of biological activities such as antimicrobial, anti-tumor, anti-allergic, antiviral, anti-inflammatory and anticancer activities [18].

Due to the aforementioned applications of hydrazones, herein we have reported the quick, facile, and convenient synthesis of six novel hydrazones containing N, O, or S atoms derived from Chromone. Hopefully, the combination of the chromone moiety with hydrazides may provide more biologically active resulting compounds. The typical synthesis of hydrazones can be described as follows:

$$2\text{−Amino-3-formylchromone} + \text{Hydrazide} \xrightarrow{\text{Acetic Acid}} \text{Hydrazone}$$

(1)

2. Materials and Methods

2-Amino-3-formylchromone, 2-hydroxybenzhydrazide, 3-hydroxy-2-naphthoic acid hydrazide, isonicotinic acid hydrazide, 2-picolinyl hydrazide, thiophene-2-carboxylic hydrazide, and 2-furoic acid hydrazide were purchased from TCI (Japan) or J&K (China) with purity higher than 98% and used without further purification. UV-Vis spectra were recorded by using a UV-1000 spectrophotometer of Tech-comp (China). Fluorescence spectra were recorded on F-7 Fluorescence spectrophotometer (Hitachi, Japan). MALDI mass spectra were obtained on time-of-flight Ultraflex II mass spectrometer (Bruker Daltonics). $^1$H and $^{13}$CNMR spectra of hydrazones in DMSO-d$_6$ solutions were recorded on a 300 MHz Bruker AV 300 spectrometer and chemical shifts are indicated in ppm.

The equimolar mixture of 2-amino-3-formylchromone and hydrazine derivative (i.e., 2-hydroxybenzhydrazide, 3-hydroxy-2-naphthoic acid hydrazide, isonicotinic acid hydrazide, 2-picolinyl hydrazide, thiophene-2-carboxylic hydrazide, or 2-furoic acid hydrazide) in acetic acid was refluxed for a certain time (Table 1). After reflux, the solution was cooled to room temperature, poured into ice-water and stirred. When the precipitates started to appear, the reaction mixtures were allowed to stand for an hour to a certain time (Table 1). After reflux, the solution was cooled to room temperature, poured into ice-water and stirred. When the precipitates started to appear, the reaction mixtures were allowed to stand for a certain time (Table 1). After reflux, the solution was cooled to room temperature, poured into ice-water and stirred. When the precipitates started to appear, the reaction mixtures were allowed to stand for a certain time (Table 1). After reflux, the solution was cooled to room temperature, poured into ice-water and stirred. When the precipitates started to appear, the reaction mixtures were allowed to stand for a certain time (Table 1). After reflux, the solution was cooled to room temperature, poured into ice-water and stirred.

| No. | Compd. | Solvent | Time(min) | Color | Yield (%) |
|-----|--------|---------|-----------|-------|-----------|
| 1   | CBH    | Acetic acid | 9         | White | 72        |
| 2   | CNH    | Acetic acid | 1         | Yellow| 81        |
| 3   | CISNH  | Acetic acid | 25        | Yellow| 69        |
| 4   | CPH    | Acetic acid | 25        | Yellow| 73        |
| 5   | CTPH   | Acetic acid | 25        | Yellow| 65        |
| 6   | CFH    | Acetic acid | 25        | Yellow| 70        |

3. Results

In this study, different hydrazides were used such as 2-hydroxybenzhydrazide (CBH), 3-hydroxy-2-naphthoic acid hydrazide (CISNH), isonicotinic acid hydrazide (CISH), 2-picolinyl hydrazide (CPH), thiophene-2-carboxylic hydrazide (CTPH), and 2-furoic acid hydrazide (CFH) for synthesis of hydrazones. The results of the study have revealed that it took only 9 min for CBH to obtain maximum white precipitates of the reaction mixture. On the other hand, the

Table 1: Reaction conditions for the 6 hydrazones.

| Serial no | Compd. | Calculated molecular mass | Observed molecular mass |
|-----------|--------|---------------------------|-------------------------|
| 1         | CBH    | 323.302                   | 323.592                 |
| 2         | CNH    | 373.360                   | 373.531                 |
| 3         | CISNH  | 308.291                   | 308.676                 |
| 4         | CPH    | 308.291                   | 308.457                 |
| 5         | CTPH   | 313.331                   | 313.487                 |
| 6         | CFH    | 297.265                   | 297.280                 |

Table 2: MALDI mass data of the six synthesized hydrazones.

| Serial no | Compd. | Conc. (μM) | Excitation (nm) | Emission (nm) |
|-----------|--------|------------|-----------------|---------------|
| 1         | CBH    | 100        | 374.0           | 458.0         |
| 2         | CNH    | 10         | 374.0           | 458.0         |
| 3         | CISNH  | 10         | 373.0           | 459.0         |
| 4         | CPH    | 10         | 390.0           | 458.2         |
| 5         | CTPH   | 10         | 374.0           | 456.4         |
| 6         | CFH    | 100        | 273.0           | 455.8         |
hydrazones through CNH was appeared with greenish precipitates in the reaction flask within one minute. The stirring of reaction mixture on heat was done to obtain maximum precipitates for few minutes. But it was not happened during the synthesis of hydrazones of CISNH, CPH, CTPH, and CFH. The precipitates were not appeared during reflux. In these reactions, a clear solution was observed for 25 min. After reflux, the solutions were cooled at room temperature, poured into ice-water, and stirred. When the precipitates started to appear, the reaction mixtures were allowed to stand for an hour to afford maximum precipitates. The precipitates were then filtered, dried, and characterized. Structures of the precursors and synthesized hydrazones are listed in Table 6.

The results obtained through MALDI mass are well consistent with the molecular weights of these six hydrazones, as shown in Table 2. The λmax and εmax values of these six hydrazones were calculated according to their UV-Vis spectra. Fluorescent properties of the hydrazones were also studied and their excitation and emission wavelengths are mentioned in Table 2. Furthermore, FTIR, 1H and 13CNMR spectral data of the hydrazones confirmed the proposed structures of hydrazones.

4. Discussion

Detailed principle peaks on the FTIR and 1H NMR spectra are listed in Tables 4 & 5, respectively. The signal at chemical shifts (δ, ppm) of 11.93-12.34 in 1H NMR spectra are assigned to the –NH group, concomitant with the observation of rapid loss of these signals. Same is the case with -NH2 groups whose peaks of both protons signals at chemical shifts of 9.28-9.88. The signals at δ of 11.98 ppm and 11.50 ppm are assigned to the aromatic –OH protons of CBH and CNH, respectively. The resonance peaks between 8.91 ppm to 9.08 ppm in the spectra are assigned to the azo-methine (-CH=N-) of these hydrazones. Signals at δ 6.70-8.79 are assigned to the aromatic protons. In 13CNMR spectra of these hydrazones, four key resonance signals were observed. These are δ 153.0-153.4 for azomethine (-CH=N-), carbonyl carbon of chromone ring roughly at δ 162.9-165.0, carbon of chromone ring attached to carbon of azomethine at δ 92.6-92.8, and δ 173.3-173.7 for the carbon (–C-NH2) on the chromone ring in all hydrazones. The signals of carbonyl carbons from hydrazine motifs were observed roughly at δ 162.9, 160.7, 150.4, 160.1, 157.3, and 145.7 from CBH, CNH, CISNH, CPH, CTPH, and CFH, respectively. The detail of other carbons in all hydrazones is described as following: Six carbons on the benzene ring of chromone of CBH are shown at δ 145.6, 133.9, 128.1, 125.3, 121.8, and 117.6. Three carbons on chromone ring are δ 173.7, 165.0, and 92.6. Six carbons on the benzene ring having –
Table 6: Chemical structures of reactants and hydrazones in this work.

| Reactant | Hydrazone                                                                 |
|----------|---------------------------------------------------------------------------|
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | 2-amino-4-oxo-4H-chromene-3-carbaldehyde (E)-N'((2-amino-4-oxo-4H-chromen-3-yl)methylene)-2-hydroxybenzohydrazide |
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | 2-hydroxybenzohydrazide                                                   |
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | 3-hydroxy-2-naphthohydrazide                                               |
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | Isonicotinohydrazide                                                      |
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | Picolinohydrazide                                                          |
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | Thiohene-2-carbohydrazide                                                  |
| 2-amino-4-oxo-4H-chromene-3-carbaldehyde | Furan-2-carbohydrazide                                                     |
The successful syntheses of the 6 hydrazones mentioned above. Six carbons on the benzene ring of chromone of CNH are shown at δ 160.1, 133.9, 125.3, 119.0, 116.9 and 115.2. Six carbons on the benzene ring of chromone of CISNH are shown at δ 150.4, 133.4, 129.0, 121.1, 121.1, and 117.1. Three carbons on chromone ring are shown at δ 173.5, 163.9, and 92.6. Ten carbons on the naphthyl ring are shown at δ 145.7, 129.0, 127.1, 125.9, 125.2, 125.2, 124.1, and 110.9. Six carbons on the benzene ring of chromone of CFH are shown at δ145.7, 128.7, 126.9, 125.0, and 116.8. Three carbons on the chromone ring are at δ 173.5, 163.0, and 92.6. Five carbons on the isonicotinic ring are shown at δ133.6, 125.0, 125.0, 121.5, and 121.5. Six carbons on the benzene ring of chromone of CPH are shown at 150.0, 135.2, 127.1, 125.0, 122.2, and 117.1. Three carbons on chromosome ring are at δ 173.4, 163.1, and 92.8. Five carbons on the pyridine ring are shown at δ 148.9, 146.1, 134.9, 125.0, and 122.2. Six carbons on the benzene ring of chromone of CTPH are shown at δ 144.2, 128.5, 125.3, 125.3, 121.8, and 117.1. Three carbons on the chromosome ring are at 173.4, 162.9, and 92.8. Four carbons on the thiophene ring are shown at δ 138.1, 133.5, 131.6, and 128.5. Six carbons on the benzene ring of chromone of CFH are shown at δ 133.4, 125.2, 125.2, 125.2, 121.7, and 116.8. Three carbons on the chromosome ring are at δ 173.3, 163.0, and 92.8. Four carbons on the furan ring are shown at δ145.7, 145.7, 114.5, and 112.2. These spectroscopic data confirmed the successful syntheses of the 6 hydrazones mentioned above. The λmax (nm) and emax values of these six hydrazones were calculated according to their UV-Vis spectra, the λmax are in the range of 344 to 351 nm and εmax was from 1.50 x 104 to 3.26 x 105 cm⁻¹ M⁻¹.

5. Conclusions
This study highlighted the synthesis and spectroscopic characterization of 6 novel hydrazones. The hydrazones were quickly synthesized through convenient and facile approach. This study reported the synthesis of CBH in 9 min. On the other hand, CNH was synthesized in 1 min only. After the reflux of 25 min, other 4 hydrazones were synthesized. The importance of these hydrazones can be realized in live cell imaging for detection of metal ions. These compounds are quite beneficial for their role as chemo sensors. As a future perspective of this study, these hydrazones containing oxygen, sulfur, and nitrogen atoms may lead biologists for its applications in biomedical fields.

Data Availability
No data were used to support this study.

Conflicts of Interest
There is no conflict of interest.

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