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Synthesis, Characterization and study of Some New Heterocyclic Compounds For Imidazolidine-dione Derivatives.

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ABSTRACT

Different N-heterocyclic substituted derivatives of 5,5-dimethylhydantoin have been synthesized. The two nitrogen atoms have been alkylated to form N-carboxymethyl followed by cyclization reaction to form heterocyclic/substituted aryl group (oxazole, imidazole and oxadiazole derivatives). Prepared compounds have been identified by using FT-IR and ^{1}HNMR and the fluorescence quantum yields of these compounds is calculated ,after calculated of $\lambda_{exc.}$, $\lambda_{em.}$ and its absorption at $\lambda_{exc.}$ for compounds by Spectrofluorophotometer and UV/VIS Spectrophotometer respectively.

Keywords: 5,5-substituted imidazolidine-Dione, Hydantoin derivatives, 1,3-Oxazole, Imidazol, Oxadiazole and Fluorescence compounds.

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INTRODICTION

Imidazolidine-Dione (hydantoin) find important applications as medicinal (anticonvulsant drugs in the treatment of epilepsy [1,2], anticancer [3], antiarrhythmic [4,5] and antitumor [6] drugs) and as Agrochemicals (bactericides and fungicides) [7]. Oxazole derivatives have activities such as antibacterial, antifungal, Pesticidal, anti-tuberculosis, anti-inflammatory and antitumor [8-11]. Imidazole is the main structure of some well-known components of human organisms such as amino acid histidine, histamine, purines, Vit-B12, biotin, present in the structure of many natural or synthetic drug molecules, for example (azomycin, cimetidine and Metronidazole) [12]. 1,3,4-Oxadiazole derivatives are reported to show the wide range of biological activities, which include anti- antibacterial [13], inflammatory [14], anticonvulsant [15-16], CNS stimulant [17] and antihypertensive [18]. Fluoresces compounds have many applications such as Lighting, analytical chemistry [19], spectroscopy [20], Biochemistry and medicine [21], Microscope and Forensics[22].

MATERIALS AND METHODS

All the chemical were purchased from Sigma Aldrich,BDH and Merck. Melting point determinations were performed by the open capillary method using a SMP30 melting point apparatus and are reported uncorrected. The F T - IR spectra (KBr-discs) were recorded with a IRAFFINITY-1 CE Shimadzu spectrometer. ^{1}H NMR spectra were recorded on a jeol 400-Hz NMR spectrophotometer operating at 400 MHz for ^{1}H measurements.Spectrofluorophotometer RF-1501 (Shimadzu).UV-6100 PC Double beam Spectrophotometer,EMCLAB,Germany. Thin layer chromatography was performed on pre-coated sheets with a 0.25 mm layer of Silica Gel GF254 of the Merck company.

Synthesis 2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl) diacetic acid (M):

Compound H (5,5-dimethylhydantoin) (0.05mole, 6.41g) Smelting with Bromoacetic acid (0.1mole, 9.45g) for (1hr) then added a solution of (Sodium hydroxide (8g) dissolved in distilled water (20mL)) and the refluxing was continued for (5 hrs). This reaction was monitored by TLC. Then decant to distilled water (150mL) and acided solution of hydrochloric acid (10%).Then, the solvent evaporated in reduced pressure (by rotary) and recrystallized with absolute ethanol. Color: crystalline white; Yield: 52%; m.p. 220-222 °C ; IR (v, cm^{-1}): brod 3,400-2,990 ($OH_{carboxyl}$),1,707($C=O_{carboxyl}$) ,2,987-2,848 (C-Haliph); ^{1}HNMR (400 MHz, DMSO-d_6) δ(ppm): 1.27 (S , 6H, $-CH_3$) , 3.76 and 3.79 (S, 4H , $-CH_2$-CO) , 8.20 (s , 2H, $-OH_{carboxyl}$) ; $C_9H_{12}N_2O_6$ (m.w. 244.20). TLC Rf = 0.62 (DCM: n-hexane).

Synthesis 2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)diacetyl chloride (M_1):

Compound M (0.01mole,2.44g) dissolved in thionyl chloride (25mL) and refluxing was continued for (3 hrs). Then, the excess Thionyl chloride evaporated in reduced pressure by rotary. Color: pale yellow; Yield: 94; m.p. : oily ; IR (v, cm^{-1}): 2,993-2939 (C-Haliph),1,720 sharp (C=Oacid chloride), 759 (CO-Cl). $C_9H_{10}Cl_2N_2O_4$ (m.w. 281.09) .

Synthesis (2,2'-((2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)bis(acetyl))bis(azanediyl))diacetic acid (M_2):

Compound M_1 (0.01mol) dissolved in (5mL) dioxane was added to a stirring solution of glycine (1.4g , 0.02mol) and sodium hydroxide (20 mL, 10% solution). Then, the reaction mixture was stirring over night. This reaction was monitored by TLC. After that, the solution was acidified with conc. HCl and the combined solution was extracted with diethyl ether (50mL) four times the solutions (organic phase) the product was collected. Color: crystalline white; Yield: 71%; m.p. 198-202 °C ; IR (v, cm^{-1}): 3,429-2,985 brod ($OH_{carboxyl}$) , 3,367 (NH) , 1,716 ($C=O_{carboxyl}$) , 1,633 ($C=O_{amid}$) ; ^{1}HNMR (400 MHz, DMSO-d_6) δ(ppm):1.28 (S , 6H, $-CH_3$) , 3.82 (S, 4H, N-CH_2-CO), 8.25 (t, 2H, -CO-NH) , 3.81 (d, 4H , $-CH_2$-CO), 10.57(S, 2H, $-OH_{carboxyl}$) ; $C_{13}H_{18}N_4O_8$ (m.w. 358.30). TLC Rf = 0.75 (acetone: n-hexane).

Synthesis (M_{3-4}):

Compound M_2 (0.01 mol) dissolved in acetic acid (10 ml) and acetic anhydride (40 ml) later aromatic aldehyde (p-hydroxy and p-chlorobenzaldehyde) (0.02 mol) was added and the refluxing was continued for (7 hrs). This reaction was monitored by TLC.Then After evaporating the solvent under reduced pressure and recrystallized from absolute ethanol and filtered.

1,3-bis(((E)-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-dimethylimidazolidine-2,4-dione (M3) : Color:dark yellow **;**Yield:83%; m.p 178-182 °C; IR (v, cm-1): 2,966- 3,441 brod (OH_{phenol}) , 3,018 (C-Har), 2,926 – 2,880 (C-Haliph), 1,645 (C=O) , 1.708 (C=O oxazole), 1.600 (C=Calkene), 1,280 (C-O); ^{1}HNMR (400 MHz, DMSO-d_6) δ (ppm) 1.6 (S , 6H, -CH_3), 4.55 (S, 4H, N-CH_2-), 6.94 (S, 2H, =CH-), 7.56 (d , 4H, CH)ar, 7.77 (d, 4H, =CH-)ar, 8.00 (d, 2H,- CH=) , 10.00 (S , 2H , -OH)ph. ; $C_{30}H_{24}N_6O_{11}$ (m.w 645)**.** TLC R*f* = 0.74 ($CHCl_3$: n-hexane).

1,3-bis(((E)-4-(4-chlorobenzylidene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-dimethylimidazolidine-2,4-dione (M4): Color: light brown **;**Yield:44%; m.p 196-198 °C; IR (v, cm-1): 3,049 (C-Har) , 2,943 – 2,875 (C-Haliph), 1.795 (C=O oxazole), 1.593 (C=C alkene), 1,212 (C-O); ^{1}HNMR (400 MHz, DMSO-d_6) δ (ppm) 1.25 (S , 6H, -CH_3), 3.52 (S, 4H, N-CH_2-), 7.46 (S, 2H, =CH-) , 7.72 (d, 4H, CH)ar, 7.879 (d, 4H, =CH-)ar ; $C_{27}H_{20}Cl_2N_4O_6$ (m.w 567.38). TLC R*f* = 0.52 (DCM: ethyl acetate).

Synthesis of 1,3-bis(((E)-1-amino-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)-5,5-dimethylimidazolidine-2,4-dione (M5):

Compound (M4) (0.01 mole) dissolved in dry benzene (10ml) and Hydrazine hydrate 80% (20 ml) was added to this mixture, The reaction mixture was refluxed for (25 hrs).This reaction was monitored by TLC. Then, the mixture was cooled to room temperature, benzene was removed by rotary, the product was collected and recrystallized from absolute ethanol. Color: red; Yield: 67%; m.p Gamy; IR (v, cm-1): 2,944-3,435 brod (OH_{phenol}), 3,305–3,167 (NH_2) , 3,068 (C-Har), 2,960-2,804 (C-Haliph.), 1,629 (C=O), 1,514-1,450 (C=Car); ^{1}HNMR (400 MHz, DMSO-d6) δ (ppm) 1.75 (S , 6H, -CH_3), 3.65 (S, 4H, N-CH_2-), 6.75 (S, 2H, =CH-), 6.34-6.751 (dd,8H, CHar), 9.00 (S , 2H , -OH)ph. , 7.62 (S, 4H, N-NH_2). $C_{27}H_{26}N_8O_6$ (m. w 558.55). TLC R*f* = 0.40 (DCM: n-hexane).

Synthesis of diethyl 2,2'-(4E,4'E)-2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)bis(methylene)bis(4-(4-hydroxybenzylidene)-5-oxo-1H-imidazole-2,1(4H,5H)-diyl)bis(azanediyl)diacetate (M6) :

The compound (M5) (0.01 mol) was refluxed with (0.02 mol) of sodium in (hot) absolute ethanol for (2hrs). This reaction was monitored by TLC. Then, ethyl bromoacetate (3.62g, 0.02 mol) was added and refluxed for (5hrs). After remaining solution concentrated in vacuo. Color: white; Yield:50%; m.p 258-262 °C; IR (v, cm-1): 2,941-3,446 brod (OH_{phenol}) , 2,985 (C-Har), 2,941 – 2,800 (C-Haliph), 1880 (C=Ooxazole), 1.608 (C=Calkene), 1,224 (C-O); ^{1}HNMR (400 MHz, DMSO-d6) δ (ppm) 0.92 (S , 6H, -CH_3), 4.20 (S, 4H, N-CH_2-), 7.72 (S, 2H, =CH-), 7.80 (d, 4H, CH)ar, 8.11 (dd, 4H, =CH-)ar, 8.41 (d, 2H,-CH=), 10.01 (S , 2H , -OH)ph. , 3.23 (d, 4H,N-CH_2-CO) ,4.12 (q, 4H,O-CH_2) , 1.18 (t, 6H, OCH_2-CH_3) ; $C_{35}H_{38}N_8O_{10}$ (m.w 730.72). TLC R*f* = 0.36 (DCM: petroleum ether).

Synthesis of 2,2'-(((4E,4'E)-2,2'-((4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)bis(methylene))bis(4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazole-2,1-diyl))bis(azanediyl))di(acetohydrazide) (M7):

Compound (M6) (0.01 mole) dissolved in absolute ethanol (25 ml) and Hydrazine hydrate (0.02 mole) was added to a mixture, The reaction mixture was refluxed for (8 hrs). This reaction was monitored by TLC. Then, the excess solvent evaporated in reduced pressure. Color:Yellow; Yield: 60%; m.p oily; IR (v, cm-1): 3,444-2,935 brod (OH_{phenol}) , 3,421 – 3,313 (NH2), 3,062 (C-Har), 2,935-2,880 (C-Haliph.), 1,672 (C=O), 1,541-1,417 (C=Car) ; ^{1}HNMR (400 MHz, DMSO-d6) δ (ppm) 1.89 (s , 6H, -CH_3), 3.72 (S, 4H, N-

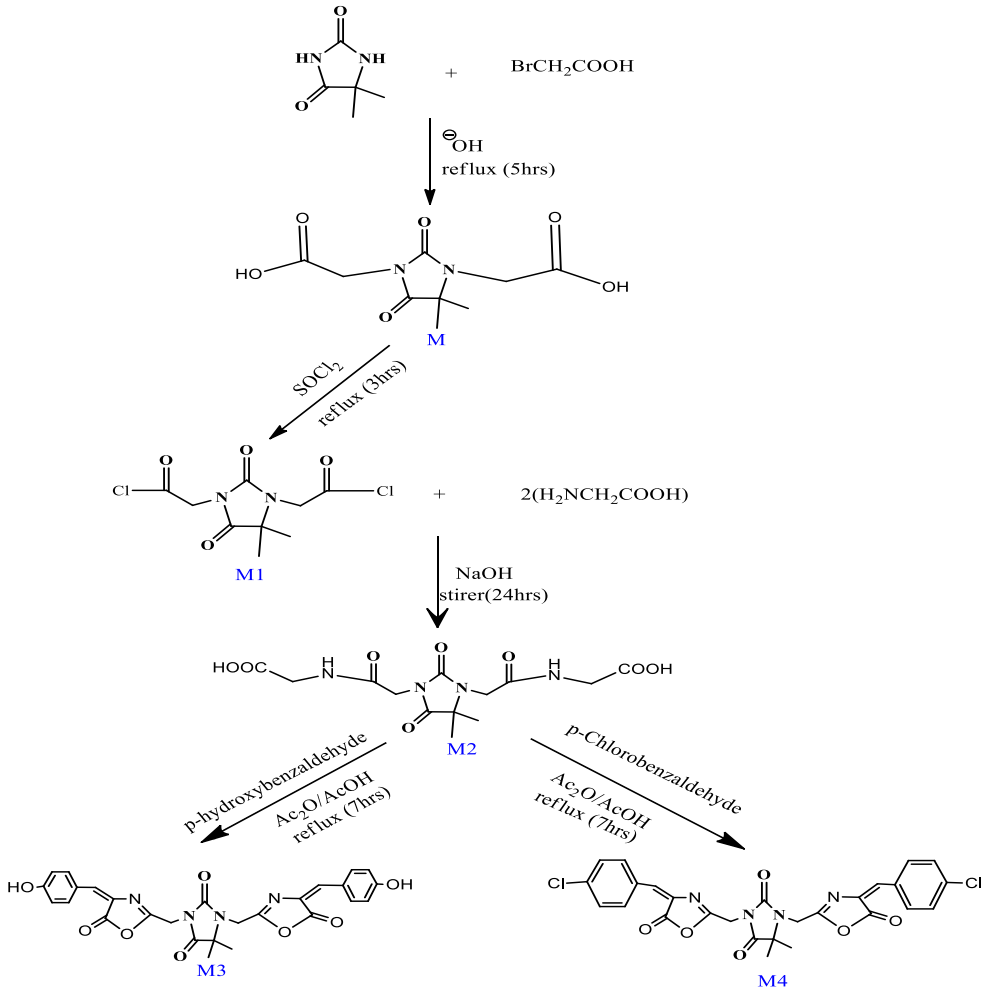
CH_2-), 6.66 (S, 2H, =CH-), 6.33-6.98 (dd,8H, CHar), 9.42 (S , 2H , -OH)ph. , 8.27 (t, 2H, NH) , 1.88 (S, 2H, NH) , 2.2 (d, 4H, N-NH_2). $C_{31}H_{34}N_{12}O_8$ (m. w 702.68). TLC R*f* = 0.32 (benzene: methanol).

Synthesis of 1,3-bis(((E)-4-(4-hydroxybenzylidene)-1-((5-mercapto-1,3,4-oxadiazol-2-yl)methylamino)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl) 5,5dimethylimidazolidine-2,4-dione (M8) :

Carbon disulfide (0.02 mole) added to mixture of compound (M7) (0.01mole) and potassium hydroxide (0.02 mole) dissolved in absolute ethanol (30 ml), refluxed for (3 hrs) This reaction was monitored by TLC, the excess solvent evaporated by rotary, the product was collected and dissolved in distilled water (200 ml), PH of the solution was (5.5-6.5) by HCl (10%) the precipitate was filtered, washed with distilled water and recrystallized from methanol to afford the desired compound. Color:light green; Yield: 54%; m.p 76-78 ˚C ; IR (v, cm-1): 2,968-3,441 brod (OH_{phenol}) , 3248 – 3151 (NH), 3,037 (C-Har), 2,968-2,835 (C-Haliph.), 2.559 (S-H), 1,612 (C=O), 1,570-1,421 (C=Car); ^{1}HNMR (400 MHz, DMSO-d6) δ (ppm) : 1.2 (S,6H,-CH_3), 4.3 (S, 4H, N-CH_2-), 1.88 (S, 2H, NH) , 4.09 (d, 4H, N-CH_2-), 6.49 (S, 2H, =CH-), 6.70-7.89 (dd,8H, CHar), 9.88 (S , 2H , -OH)ph. , 12.2 (S, 2H, -SH). $C_{33}H_{30}N_{12}O_8S_2$ (m. w 786.8). TLC R*f* = 0.28 ($CHCl_3$: n-hexane).

RESULTS AND DISCUSSION

The designated compounds were synthesized according to Scheme 1:



Scheme 1. The synthesis of compounds M-M4.

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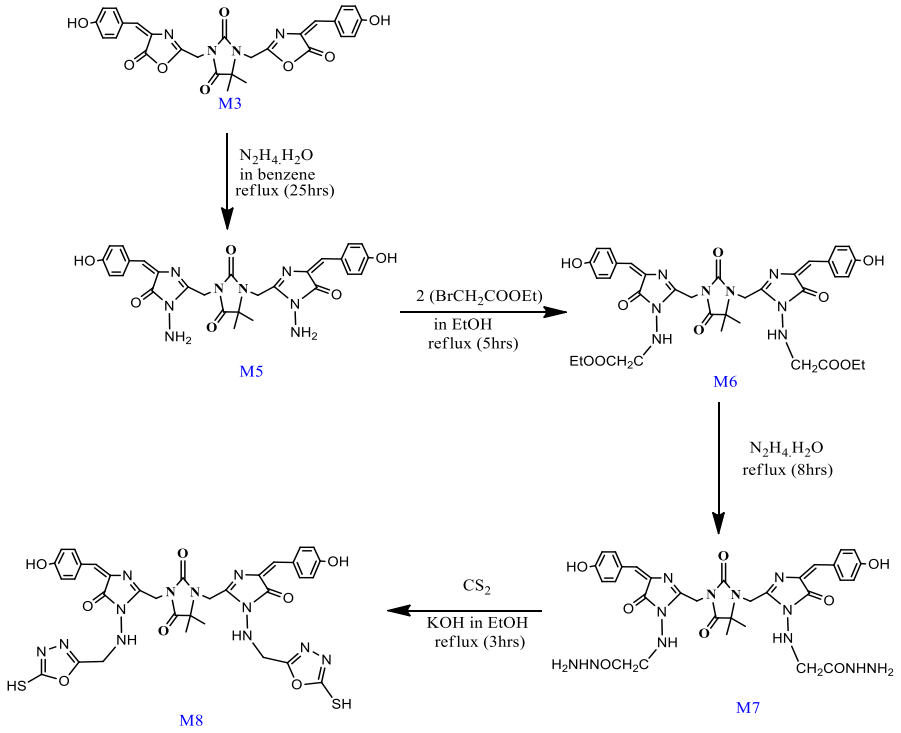

Scheme 2. The synthesis of compounds M5-M8.

The reaction of smelting of 5,5-dimethylhydantoin (H) with bromoaceticacid in basic media given 2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)diacetic acid (M). The IR spectrum of the product indicated by appear brod band (3400-2990) cm-1due to hydroxyl group of carboxylic derivatives . In the ^{1}H-NMR spectrum , the proton signals at 1.27ppm due to 6H of two methyl group , new signal at 3.76-3.79 ppm for 4H of CH_2-CO and 8.20 ppm for hydroxyl group . 2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)diacetyl chloride (M_1) identification by absence of band of hydroxyl group in compound (M) at 3400-2990 cm-1 and appear new sharp band at 1720 and 759 cm^{-1} refers to carbonyl of acid chloride and chloride bond consecutively in FT-IR spectrum . Reaction of (M1) with amino acid (Glycine) afforded (2,2'-((2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)bis(acetyl))bis(azanediyl))diacetic acid (M2). The IR spectrum of the product indicated by absence of absorption bands due to carbonyl of acid chloride at 1,784 cm^{-1} and the presence of a OH absorption band at 3,429-2,985 cm^{-1} and showed two sharp absorption band, the first appears at 1,716 cm^{-1} refers to carbonyl function of the carboxylic acid and observed at 1,633 cm^{-1}, was assigned to a C=O stretching frequency of amide carbonyl group. In the ^{1}H-NMR spectrum, the proton signals due to (-CO-NH) and ($OH_{carboxyl}$) resonated at 8.25 ppm and 10.57 respectively, integrating for two protons. Compound M3 and M4 1,3-bis(((E)-4-(argiomethylene)-5-oxo-4,5-dihydrooxazol-2-yl)methyl)-5,5-dimethylimidazolidine-2,4-dione prepared by oxidative cyclization of compound M2 with aromatic aldehydes (parahydroxy and parachloro benzaldehyde) .The structure of compound M3 was indicated by appear new signal at (3,018 and 1,485) Cm^{-1} refers to C-Har and C=Car respectively due to the cyclization reaction and addition of aromatic part. The structures of compounds M4 were indicated by the absence of the characteristic OH stretching at (3,429-2,985) cm^{-1} in addition to the absorption bands for the NH at 3,367 cm^{-1}, also an increase in the absorption band for the carbonyl group have been made to be 1,625 cm^{-1} also appear new signal at (3,035 and 1,485) Cm^{-1} refers to C-Har and C=Car respectively . The ^{1}H-NMR spectra of compounds M3 and M4 showed new signals at (7.56 -7.77) and (7.46-7.87) ppm respectively integrated for four protons assigned to aryl group , also a single peak at 7.46 ppm appeared suitable to (C=CH Ar) group with appear signal at 9.42 ppm for hydroxyl of phenol group in compound M3 . The key intermediate 1,3-bis(((E)-1- amino-4-(4-substitutedbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-2-yl)methyl)- 5,5-dimethylimidazolidine-2,4-dione M5 was prepared from the reaction of hydrazine 80% with compounds M3 . The spectra exhibited

an NH_2 is stretching vibration at 3,441-3,234 cm^{-1} and decrease C=O stretching vibrations at 1,645 cm^{-1}. The appearance of single peak at 7.62 ppm in the ^{1}H-NMR spectra of compound M5 could be a good prove for the substitution of oxygen atom by N-NH_2 group. Alkylation of compound M5 with ethyl bromoacetate (Scheme1) gave diethyl 2,2'-(4E,4'E)-2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)bis(methylene)bis(4-(4-hydroxybenzylidene)-5-oxo-1H-imidazole-2,1(4H,5H)diyl)bis(azanediyl)diacetate (M6) identification by absence of characteristic NH_2 stretching at (3,305-3,167) cm^{-1} and appear new signal at 1716 cm^{-1} for carbonyl of ester and New signal for $COCH_2CH_3$ ester at 1.18 and 4.12 ppm in H^1NMR spectrum. The formation of compounds 2,2'-(4E,4'E)-2,2'-(4,4-dimethyl-2,5-dioxoimidazolidine-1,3-diyl)bis(methylene)bis(4-(4-hydroxybenzylidene)-5-oxo-1H-imidazole-2,1(4H,5H)-diyl)bis(azanediyl)diacetohydrazide (M7) was confirmed by the appearance of the asymmetrical absorption band at 3,441-3,234 cm^{-1} for the NH_2 group. The ^{1}H-NMR spectra of compounds M7 has shown the signal at 8.27 ppm for NH and 2.2ppm for NH_2. addition of carbon disulfide and cyclization of compound M7 syntheses new oxazole derivatives substuted by thiole (M8) and identification by absence band of NH_2 at 3,421 – 3,313 cm^{-1} and appear new band for SH at 2,559 cm^{-1} in FTIR chart and appear new signal at 12.2 ppm for SH.

Application

The process of the internal conversion and intersystem crossing with the fluorescence or phosphorescence process,therefore it was not found the efficiency of 100%,thereby it's become necessary to calculate the quantum yield. The ratio of the number of fluorescence photons emitted to the number of photons absorbed was called the quantum efficiency of fluorescence Φf [23].

$$\Phi = \frac{\text{Number of photons emitted}}{\text{Number of photons absorbed}}$$

Quantum yields of the compound calculated by the equations below:

$$\frac{F2}{F1} = \frac{I°\varepsilon Cd\Phi 2}{I°\varepsilon Cd\Phi 1} = \frac{(area)}{(area)}$$

$$\Phi_{sample} = \frac{(area)\ standerd \times Asample}{(area)sample \times Astanded} \times \Phi_{standerd}$$

Fluorescence properties and quantum yields of the compound showed in table **(1).**

Table (1) shows λexc. , λem. And quantum yield of compounds

Compound	T (K)	$\lambda_{exc.}$ (nm)	$\lambda_{em.}$ (nm)	ϕf
M	303	275	308	0.11
M1	303	331	374	-
M3	303	386	470	0.06
M4	303	340	381	0.05
M8	303	444	479	0.17

λexc. & λem. = Excitation and emission maxima in nanometers
ϕf = quantum yields
- = ϕf <0.05

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