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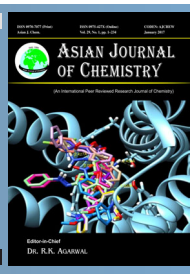

Synthesis and Properties of Some N-(2,3-Dihydrophthalazin-5-yl)amidrazones Incorporating Piperazines and Related Congeners

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A new *N*-(phthalazin-5-yl)hydrazonoyl chloride derivative (**2**) is made accessible from luminol *via* the Japp-Klingemann reaction. In presence of triethyl amine, compound **2** reacted with *N*-substituted piperazines and related *sec*-amine congeners to deliver the respective set of new *N*-(phthalazin-5-yl)amidrazones (**4a-h**) in fair yield. The chemical structures of the newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and ESI-HRMS spectral data. However, the amidrazones (**4a-e**) were found to display weak to moderate activity against breast cancer cell line (MCF-7) with $MIC_{50} \approx 25$-100 μM/mL.

Keywords: Luminol, Hydrazonoyl chloride, *N*-(Substituted)piperazines, *N*-(Pthalazin-5-yl)amidrazones.

INTRODUCTION

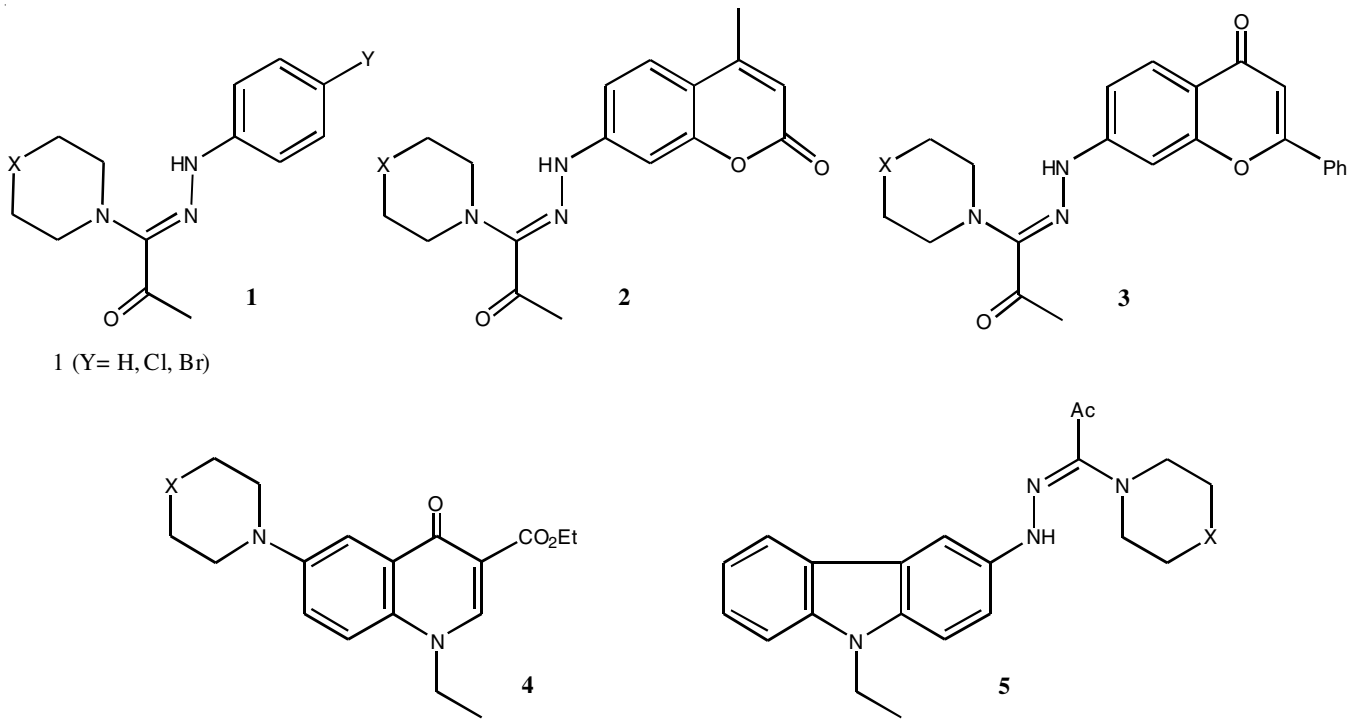
5-Amino-2,3-dihydro-1,4-phthalazinedione (luminol), synthesized in 1928 [1], is a strong chemiluminescent compound, characterized by blue light emission when mixed with a suitable oxidizing agent [2]. Luminol emits fluorescence in neutral, or acidic solutions and in basic solutions in the presence of an oxidant [3]. It has been widely used in various areas such as pharmaceutical, environmental or even life sciences [4]. Luminol's most known application is in Crime Scene Investigations. It reacts with iron found in hemoglobin and gives characteristic emission [5]. This application is widely known as "CSI" [6]. Luminol is used also in several special applications *e.g.*, determination of hydrogen peroxide concentration in waste water treatment [7], protein analysis [8], toxic matal (Cd, Cr, Pb, Zn, *etc.*) analysis in water, food and other objects [9] and determination of corticosteroids using flow injection [10].

On the other hand, piperazine derivatives have drawn considerable attention from organic and medicinal chemists. Pepirazine-based compounds have been employed as antibacterial [11], antidepressant [12] and antitumor [13] drugs and as α-adrenoceptor antagonists [14]. Recently, *N*1-aryl (piperazine-1-yl)amidrazones, exemplified by **1a** (Fig. 1), were reported to exhibit significant activity against a number of cell lines, especially Leukemia, breast, non-small-cell lung and CNS cancer ($IC_{50} \approx 4$ μM) [15]. More recently, we have prepared several sets of amidrazones incorporating selected pharmacophoric groups and evaluated their biological activities. Examples, shown in Fig. 1, include amidrazones derived from coumarin (**1b**) [16], flavone (**1c**) [17] and (**1d**) [18], quinolone (**1e**) [19] and carbazole (**1f**) [20]. Compounds **1b-1d** displayed excellent antitumor activity, while **1e** and **1f** showed moderate- to high antibacterial potency.

With the preceeding information in mind, we anticipated that a hybrid structure based on amidrazone-phthalazine-1,4-dione (luminol) might display interesting biological activity such as antitumor and/or antibacterial activity. Accordingly, we report herein on the synthesis and bioassay of a selected set of new phthalazin-5-yl amidrazons (**4a-h**) as summerized in **Scheme-I**.

EXPERIMENTAL

5-Amino-2,3-dihydro-1,4-phthalazinedione (luminol), 3-chloro-2,4-pentanedione, piperidine, morpholine, thiomorpholine, 1-(methyl)piperazine, 1-[(hydroxyethyl)]piperazine, 1-(phenyl)piperazine, 1-[4-hydroxyphenyl]piperazine and 1-[(2-pyridyl)]piperazine were purchased from Acros and were used as received. Melting points were determined on a Stuart scientific melting apparatus in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III), with TMS as the internal standard. Chemical shifts are expressed in δ units; *J* values for ^{1}H-^{1}H coupling constants are given in Hertz. High resolution mass spectra (HRMS) were acquired by electrospray ionization (ESI) technique with the aid of Bruker APEX-4 (7 Tesla) instrument. The samples were dissolved in chloroform and infused



Compounds **1-5** (X= CH_2, O, S, *N*-H, *N*-alkyl, *N*-aryl)

Fig. 1. Cyclic amine-substituted amidrazones

using a syringe pump with a flow rate of 2 µL/min. External calibration was conducted using an arginine cluster in a mass range of *m/z* = 175-871.

***N*-(1,4-Dioxo-1,2,3,4-tetrahydrophthalazin-5-yl)-2-oxopropanehydrazonoyl chloride (2):** This new chlorohydrazone was prepared by the following two-step procedure. **Step (i):** To a solution of 3-aminophthalhydrazide **(1)** (5.67 g, 0.032 mol) in 6 N aqueous HCl (50 mL) was added, dropwise, a solution of sodium nitrite (2.6 g, 38 mmol) in water (4 mL) with efficient stirring at -1 to 3 °C. Stirring was continued for 20-30 min. and the resulting fresh cold diazonium chloride solution was used immediately as such for the following coupling reaction. **Step (ii):** A cold (-5 °C) freshly prepared solution of the diazonium chloride (**1A**) (0.032 mol) was poured onto a cold solution (-10 to -4 °C, ice-salt bath) of 3-chloro-pentan-2,4-dione (4.3 g, 0.032 mol) in ethanol-water (50 mL, 1:1 v/v) containing sodium acetate (9.6 g), with vigorous stirring. The resulting yellowish-coloured mixture was further stirred until a solid precipitate was formed (5-10 min.). The reaction mixture was then diluted with cold water (200 mL), the solid product was collected by suction filtration, washed several times with cold water, dried and recrystallized from ethanol. Yield: 91 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.56 (s, 3H, $COCH_3$), 7.55 (d, *J* = 7.5 Hz, 1H, H-8), 7.88 (dd, *J* = 7.5, 7.9 Hz, 1H, H-7), 7.92 (d, *J* = 7.9 Hz, 1H, H-6), 11.65, 11.98 (br s, 2H, N(2)-H + N(3)-H), 13.23 (s, 1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.9 (CO*C*H$_3$), 113.5 (C-4a), 115.8 (C-6), 117.4 (C-8), 126.8 (Cl-C=N-), 127.4 (C-8a), 135.4 (C-7), 143.7 (C-5), 151.9 (C-1), 161.2 (C-4), 188.5 (*C*OCH$_3$). HRMS (ESI): *m/z* = 279.02931 (calcd. 279.02904 for $C_{11}H_8{}^{35}ClN_4O_3$, $[M-H]^-$); *m/z* = 281.02674 (calcd. 281.02644 for $C_{11}H_8{}^{37}ClN_4O_3$, [M + 2 - H]$^-$).

General procedure for the synthesis of the target amidrazones (4a-h): To a cold suspension (-10 to 0 °C) of the hydrazonoyl chloride (**2**) (0.5 g, 1.80 mmol) in absolute ethanol (20.0 mL) was added, with stirring, a solution of the appropriate cyclic *sec*-amine (**3a-h**) and triethylamine (4 mL) in absolute ethanol (5 mL). Stirring was continued at 0 to 5 °C for 2-4 h and at ambient temperature for additional 4-5 h. The resulting crude solid product was collected by suction filtration, washed with water, dried and recrystallized from ethanol. Using the same general procedure, the following compounds were prepared:

5-[2-{2-Oxo-1-(piperidin-1-yl)propylidene}hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4a): Yield: 21 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.55 (m, 2H, H_2-4′), 1.70 (m, 4H, H_2-3′/H_2-5′), 2.40 (s, 3H, $COCH_3$), 2.94 (m, 4H, H_2-2′/H_2-6′), 7.40 (d, *J* = 7.6 Hz, 1H, H-8), 7.81 (dd, *J* = 7.6, 8.3 Hz, 1H, H-7), 7.91 (d, *J* = 8.3 Hz, 1H, H-6), 11.63 (br s, 2H, N(2)-H + N(3)-H), 12.83 (s, 1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.4 (C-4′), 26.2 (C-3′, C-5′, 26.5 (CO*C*H$_3$), 49.3 (C-2′, C-6′), 112.8 (C-4a), 115.2 (C-8), 115.6 (C-6), 126.9 (C-8a), 135.1 (C-7), 145.0 (C-5), 146.5 (Ac-*C*=N), 151.0 (C-1), 160.5 (C-4), 195.6 (*C*OCH$_3$). HRMS (ESI) *m/z* = 330.15571 (calcd. 330.15607 for $C_{16}H_{20}N_5O_3$ $[M + H]^+$).

5-[2-(1-Morpholino-2-oxopropylidene)hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4b): Yield: 52 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.41 (s, 3H, $COCH_3$), 3.02 (m, 4H, H_2-3′/H_2-5′), 3.78 (m, 4H, H_2-2′/H_2-6′), 7.42 (d, *J* = 7.7 Hz, 1H, H-8), 7.82 (dd, *J* = 7.7, 8.1 Hz, 1H, H-7), 7.91 (d, *J* = 8.1 Hz, 1H, H-6), 11.66 (br s, 2H, N(2)-H + N(3)-H), 12.96 (s, 1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.5 (CO*C*H$_3$), 48.3 (C-3′, C-5′), 67.1 (C-2′, C-6′), 112.9 (C-4a), 115.2 (C-6), 115.5 (C-8), 126.9 (C-8a), 135.1

(C-7), 144.8 (Ac-*C*=N), 144.8 (C-5), 151.8 (C-1), 161.3 (C-4), 195.3 (*C*OCH$_3$). HRMS (ESI) *m/z* = 330.12077 (calcd. 330.12078 for $C_{15}H_{16}N_5O_4$ [M-H]$^-$).

5-[2-(2-Oxo-1-thiomorpholinopropylidene)hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4c): Yield: 63 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.39 (s, 3H, COCH$_3$), 2.81 (m, 4H, H$_2$-2′/H$_2$-6′), 3.18 (m, 4H, H$_2$-3′/H$_2$-5′), 7.43 (d, *J* = 7.7 Hz, 1H, H-8), 7.81 (dd, *J* = 7.7, 8.2 Hz, 1H, H-7), 7.90 (d, *J* = 8.2 Hz, 1H, H-6), 11.50 (br s, 2H, N(2)-H + N(3)-H), 12.99 (s, 1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3 (CO*C*H$_3$), 27.9 (C-2′, C-6′), 50.6 (C-3′, C-5′), 113.0 (C-4a), 115.2 (C-6), 115.6 (C-8), 127.0 (C-8a), 135.1 (C-7), 144.7 (C-5), 146.1 (Ac-*C*=N), 152.1 (C-1), 161.2 (C-4), 195.3 (*C*OCH$_3$). HRMS (ESI) *m/z* = 346.09779 (calcd. 346.09793 for $C_{15}H_{16}N_5O_3S$ [M-H]$^-$).

5-[2-{1-(4-Methylpiperazin-1-yl)-2-oxopropylidene}-hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4d): Yield: 31 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.23 (s, 3H, NC*H*$_3$), 2.40 (s, 3H, COCH$_3$), 3.02 (m, 4H, H$_2$-2′/H$_2$-6′), 2.50 (m, 4H, H$_2$-3′/H$_2$-5′, hidden under DMSO), 7.41 (d, *J* = 7.6 Hz, 1H, H-8), 7.81 (dd, *J* = 7.6, 8.3 Hz, 1H, H-7), 7.91 (d, *J* = 8.3 Hz, 1H, H-6), 11.80 (br s, 2H, N(2)-H + N(3)-H), 12.77 (s, 1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.6 (CO*C*H$_3$), 46.5 (N*C*H$_3$), 47.7 (C-2′, C-6′), 55.4 (C-3′, C-5′), 112.9 (C-4a), 115.2 (C-6), 115.3 (C-8), 126.9 (C-8a), 135.0 (C-7), 144.9 (C-5), 145.4 (Ac-*C*=N), 151.9 (C-1), 161.2 (C-4), 195.5 (*C*OCH$_3$). HRMS (ESI) *m/z* = 345.16635 (calcd. 345.16696 for $C_{16}H_{21}N_6O_3$ [M + H]$^+$).

5-[2-{1-(4-(2-Hydroxyethyl)piperazin-1-yl)-2-oxo-propylidene}hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4e): Yield: 54 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.41 (t, *J* = 6.1 Hz, 2H, NC*H*$_2$), 2.51 (m, 4H, H$_2$-3′/H$_2$-5′), 2.54 (s, 3H, COCH$_3$), 2.90 (m, 4H, H$_2$-2′/H$_2$-6′), 3.03 (s, 1H, O*H*), δ 3.51 (t, *J* = 6.1 Hz, 2H, C*H*$_2$–OH), 7.58 (d, *J* = 7.7 Hz, 1H, H-8), 7.73 (dd, *J* = 7.7, 8.0 Hz, 1H, H-7), 7.87 (d, *J* = 8.0 Hz, 1H, H-6), 12.80 (br s, 2H, N(2)-H + N(3)-H), 14.77 (s, 1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.9 (CO*C*H$_3$), 44.1 (C-2′, C-6′), 51.7 (C-3′, C-5′), 58.9 (CH$_2$-OH), 61.0 (NCH$_2$), 114.7 (C-4a), 115.3 (C-6), 117.8 (C-8), 129.5 (C-8a), 133.3 (C-7), 145.7 (C-5), 145.7 (Ac-*C*=N), 156.2 (C-1), 159.4 (C-4), 188.1 (*C*OCH$_3$). HRMS (ESI) *m/z* = 375.17755 (calcd. 375.17753 for $C_{17}H_{23}N_6O_4$ [M + H]$^+$).

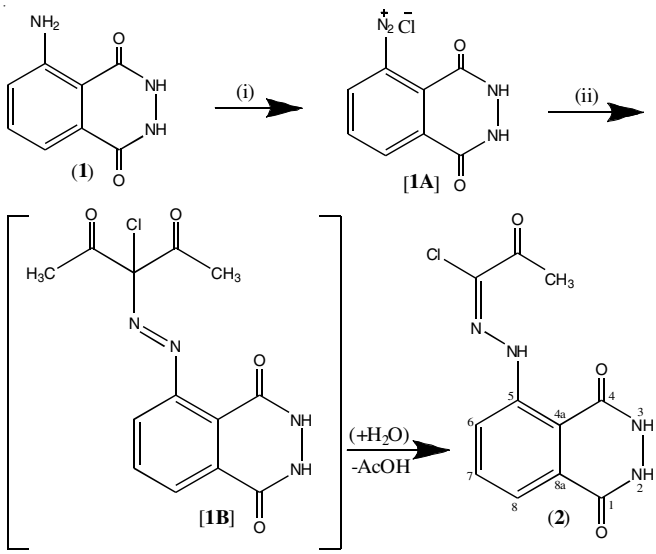
5-[2-{2-Oxo-1-(4-phenylpiperazin-1-yl)propylidene}-hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4f): Yield: 43 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.44 (s, 3H, COCH$_3$), 3.17 (m, 4H, H$_2$-3′/H$_2$-5′), 3.35 (m, 4H, H$_2$-2′/H$_2$-6′), 6.80 (pseudo t, *J* = 7.3,1H, H-4″), 6.98 (d, *J* = 8.3, 2H, H-2″/H-6″), 7.23 (pseudo t, *J* = 7.3, 2H, H-3″/H-5″), 7.42 (d, *J* = 7.7 Hz, 1H, H-8), 7.83 (dd, *J* = 7.7, 8.3 Hz, 1H, H-7), 7.93 (d, *J* = 8.3 Hz, 1H, H-6), 11.51 (br s, 2H, N(2)-H + N(3)-H), 13.01 (1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.5 (CO*C*H$_3$), 47.9 (C-3′, C-5′), 49.3 (C-2′, C-6′), 112.9 (C-4a), 115.2 (C-6), 116.0 (C-2″, C-6″), 116.3 (C-8), 119.4 (C-4″), 126.8 (C-8a), 129.4 (C-3″, C-5″), 135.2 (C-7), 144.8 (C-5), 145.3 (Ac-*C*=N), 151.6 (C-122), 151.7 (C-1), 161.3 (C-4), 195.5 (*C*OCH$_3$). HRMS (ESI) *m/z* = 407.18312 (calcd. 407.18262 for $C_{21}H_{23}N_6O_3$ [M + H]$^+$).

5-[2-{1-(4-(4-Hydroxyphenyl)piperazin-1-yl)-2-oxo-propylidene}hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4g): Yield: 34 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.42 (s, 3H, COCH$_3$), 3.15 (m, 4H, H$_2$-2′/H$_2$-6′), 3.16 (m, 4H, H$_2$-3′/H$_2$-5′), 6.70 (d, *J* = 8.6, 2H, H-2″/H-6″), 6.80 (d, *J* = 8.7, 2H, H-3″/H-5″), 7.41 (d, *J* = 7.6 Hz, 1H, H-8), 7.79 (dd, *J* = 7.6, 8.1 Hz, 1H, H-7), 7.90 (d, *J* = 8.1 Hz, 1H, H-6), 8.93 (s, 1H, O*H*), 11.51 (br s, 2H, N(2)-H + N(3)-H), 12.90 (1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.5 (CO*C*H$_3$), 48.1 (C-22, C-6′), 51.0 (C-3′, C-5′), 112.9 (C-4a), 115.2 (C-6), 115.5 (C-8), 116.0 (C-2″, C-6″), 118.3 (C-3″, C-5″), 127.1 (C-8a), 135.0 (C-7), 144.9 (C-5), 145.4 (Ac-*C*=N), 145.6 (C-1″), 151.5 (C-4″), 152.0 (C-1), 161.1 (C-4), 195.4 (*C*OCH$_3$). HRMS (ESI) *m/z* =423.17796 (calcd. 423.17753 for $C_{21}H_{23}N_6O_4$ [M + H]$^+$).

5-[2-{2-Oxo-1-(4-(pyridin-2-yl)piperazin-1-yl)propyli-dene}hydrazinyl]-2,3-dihydrophthalazine-1,4-dione (4h): Yield: 67 %, m.p.: > 330 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.54 (s, 3H, COCH$_3$), 2.95 (m, 4H, H$_2$-2′/H$_2$-6′), 3.53 (m, 4H, H$_2$-3′/H$_2$-5′), 6.66 (dd, *J* = 7.0, 5.0 Hz, 1H, H-5″), 7.55 (m, 1H, H-4″), 7.58 (d, *J* = 7.7 Hz, 1H, H-8), 7.76 (dd, *J* = 7.7, 8.2 Hz, 1H, H-7), 7.88 (d, *J* = 8.2 Hz, 1H, H-6), 8.12 (dd, *J* = 4.8, 1.7 Hz, 1H, H-622), 8.83 (d, *J* = 8.6 Hz, 1H, H-3″), 11.51 (br s, 2H, N(2)-H + N(3)-H), 14.40 (1H, C(5)-N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.9 (CO*C*H$_3$), 44.4 (C-2′, C-6′), 44.5 (C-3′, C-5′), 107.7 (C-3″), 113.8 (C-5″), 114.2 (C-4a), 115.5 (C-6), 117.7 (C-8), 128.5 (C-8a), 134.0 (C-7), 138.1 (C-4″), 144.9 (C-5), 145.0 (Ac-*C*=N), 148.0 (C-6″), 154.8 (C-1), 159.3 (C-2″), 160.0 (C-4), 188.2 (*C*OCH$_3$). HRMS (ESI) *m/z* = 408.17805 (calcd. 408.17786 for $C_{20}H_{22}N_7O_3$ [M + H]$^+$).

RESULTS AND DISCUSSION

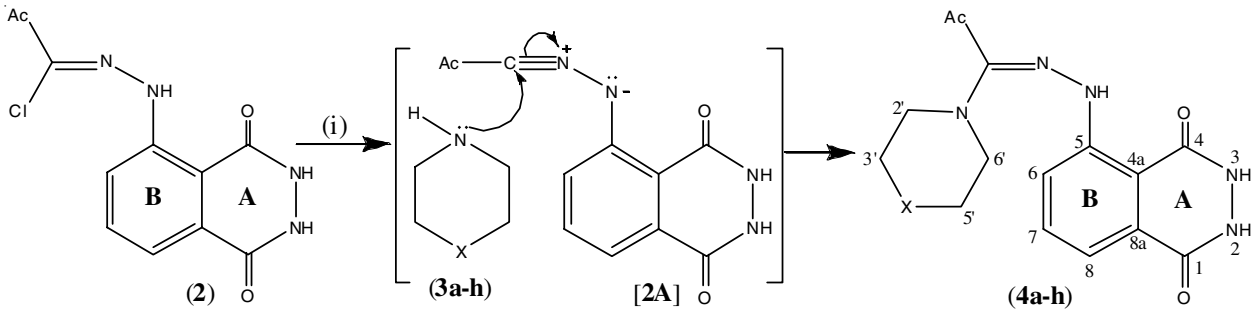
Hydrazonoyl chloride (**2**) was prepared *via* diazotization of 3-aminophthalhydrazide (**1**), followed by coupling with 3-chloro-2,4-pentanedione in basic medium (NaOAc) (**Scheme-I**). The resulting intermediate azo-compound (**1B**) suffers loss of an acetyl group, under the prevailing basic reaction conditions, to deliver the corresponding chlorohydrazone structure **2** (Japp-Klingemann reaction) [21-23].



(i) 6 N aq. HCl / $NaNO_2$ / -1 to 3 ºC

(ii) $(Ac)_2CHCl$ / aq. NaOAc + EtOH / -5 to 0 ºC

Scheme-I: Synthetic route for the hydrazonoyl chloride (**2**)



(i) NEt_3, EtOH / 0 to 20 °C

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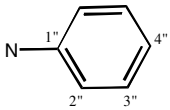
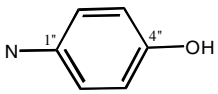
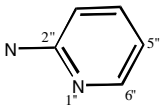
X	CH_2	O	S	NMe	NCH_2CH_2OH			

Scheme-II: Synthetic route for the amidrazones **4a-h**

Cyclic *sec*-amines **3a-h**, acting as nitrogen nucleophiles, add readily to the nitrile imine (**2A**) (generated *in situ* from the respective hydrazonoyl chloride **2** in the presence of triethylamine) to yield the corresponding *Z*-amidrazones **4a-h** (**Scheme-II**). This mode of nucleophilic addition reaction of various nucleophiles onto 1,3-dipoles is well-documented [24-29] and several adducts related to **4a-h** were obtained from the reaction of simple amines with different hydrazonoyl chlorides.

The newly synthesized compounds **2** (**Scheme-I**) and **4a-h** (**Scheme-II**) were characterized by MS and NMR spectral data. These data are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H- and ^{13}C- signal assignments to the different carbons and their attached and/or neighboring hydrogens. Thus, the ^{1}H NMR spectrum of **2** showed a singlet signal at 2.56 ppm which is attributed to the acetyl methyl protons. The two-NH protons [N(2)H, N(3)H] are exchangeable with D_2O and appear as downfield broad singlet signal at 11.98 ppm, while the exchangeable amidrazone-NH proton appears as downfield singlet signal at 13.23 ppm. The ^{1}H NMR spectra also showed three sets of signals in the range 7.55-7.92 ppm, which were assigned to the aromatic protons H-6, H-7 and H-8. The ^{13}C NMR spectrum of compound **2** revealed that all of the different carbon atoms are detectable; the keto group resonates at 188.5 ppm while the methyl carbon signal of the acetyl group appears at 25.9 ppm. DEPT-90 experiment confirmed the presence of three C-H atoms in the range 115-136 ppm.

Cell proliferation assay: Anti-MCF-7 screening assay was performed for solutions of **4a-h** in DMSO as previously described for related systems [30]. However, the amidrazones **4a-e** were found to display weak to moderate activity against breast cancer cell line (MCF-7) with $MIC_{50} \approx 25\text{-}100$ µM/mL.

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