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SYNTHESIS AND CHARACTERIZATION OF NOVEL PHTHALAZINYL HYDRAZONES OF FURAN-2-CARBALDEHYDE

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ABSTRACT

A series four new phthalazinyl hydrazones of furan-2-carbaldehyde were designed and synthesized from substituted furan-2-carbaldehyde and phthalazinyl hydrazine with good yields. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectroscopy. The synthesized hydrazones would lead the promising pharmacological properties in the future.

KEYWORDS: *Phthalazinyl hydrazone, furan-2- carbaldehyde, Meerwein arylation.*

1. INTRODUCTION:

A series four new hydrazones were designed by considering the importance of biologically active pharmacophores and prepared successfully. The pharmacodynamic potential of bioactive hydrazones is primarily due to the presence of pharmacophoric azomethine (>C=N-NH) moiety having broad biological applications such as antimicrobial [1], antimycobacterial [2], antimalarial [3], analgesic, anti-inflammatory [4], anticancer [5], anti-HIV [6], anticonvulsant [7], anti-depressant [8], vasodilator [9], alzheimer diseases [10], hypertension [11] and antiplatelet [12].

The heterocycle, furan found in many naturally occurring compounds originated from plants and marine organisms. It is a key component, in a number of biologically significant natural products. Various substituted furans are used as commercial pharmaceutical agents, flavor and fragrance compounds. Medicinal properties of Furan include anticancer [13], antidepressant [14], anti-inflammatory [15], muscle relaxant [16], antimicrobial, anti-ulcer [17], anti-parkinsonism [18], antidiuretic [19]. Polysubstituted furans can also be employed as building blocks for the total synthesis of complicated naturally occurring metabolites and as versatile starting materials for the preparation of a variety of heterocyclic and acyclic compounds.

The phthalazine and its 3-oxo derivatives (pyridazinones and phthalazinone) have attracted a great deal of attention because of the wide spectrum of their pharmacological, clinical as well and agrochemical applications [20, 21]. Phthalazine derived drug molecules which are currently available in the market under the trade name such as, Hydralazine, Dihydralazine, Budralazine, Todralazine etc. are antihypertensive; the phthalazinone derivatives such as Azelastine is used as antiasthmatic, antiallergic and antihistaminic.

The growing interest in these compounds and their potential use in medicinal applications are proved by the growing number of publications concerning the synthesis and biological evaluation of hydrazone analogues. The significant biological activity and great utility of both the heterocvclic scaffolds have encouraged us to synthesize furan substituted phthalazinyl hydrazone derivatives.

2. EXPERIMENTAL SECTION:

All the compounds and reagents were commercially available without pre-treatment. All solvents and reagents are analytically pure and no further purification was needed. Melting points were recorded in open capillary tubes and were found uncorrected. Reaction courses and product mixtures were routinely monitored by TLC on Silica gel precoated plates GF-254. IR spectra were recorded on Thermo Scientific Spectrometer. ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer using TMS as internal standard.

2.1 General procedure for the synthesis of 5-aryl furan-2-carbaldehydes (3a-c):

The substituted aniline (0.01 mole) was dissolved in a mixture of 5 ml conc. hydrochloric acid and 20 mL of water under stirring and cooled in an ice bath at 0-5 ^{o}C. A solution of sodium nitrite (0.012 mole) in water was added portion wise, keeping the temperature below 7-8 ^{o}C. The reaction mixture was left for 1h for the completion of diazotization, filtered with the help of glass wool (if any turbidity observed). Then, to the solution of furan-2-carbaldehyde (0.01 mole), the diazonium salt solution was added drop wise followed by a solution of copper chloride (0.003 mole in 5 ml of water). The temperature was raised to 30 ^{o}C by heating (if necessary) and stirred for 4-6 h. The completion of reaction was monitored by TLC. Then, the reaction mixture was left for 24 h at room temperature. The precipitate obtained was diluted and washed with water. Then the crude product was filtered, dried and recrystallized from ethanol to afford 5-aryl furan-2-carbaldehydes (3a-c).

2.2 General procedure for the synthesis of phthalazinyl hydrazones of furan-2-carbaldehyde (5a-d):

The equimolar mixture of substituted furan-2-carbaldehyde (1 mmol), phthalazin-1-yl hydrazine (1 mmol) and 2-3 drops glacial acetic acid in ethanol (10 ml) was heated at 70-80 ^{o}C for 4-6 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mass was poured into ice cold water and the product precipitated out which was filtered, washed and recrystallised from ethanol to obtain pure product (5a-d).

3. CHARACTERISATION:

1-(2-(furan-2-ylmethylene)hydrazinyl)phthalazine (5a):

Yield: 89 %; MF: $C_{13}H_{10}N_4O$; Mol.Wt.: 238.24; Colour: Brown solid; MP: 176^{o}C.
IR (cm^{-1}): 3286.02, 2921.50, 1601.13, 1586.58, 1371.62, 1243.86, 1109.44, 851.61; ^{1}H NMR (400 MH_z, $CDCl_3$) δ: 6.531 (1H, d, *J* = 3.2 Hz), 6.795 (1H, d, *J* = 3.2 Hz), 7.514-7.566 (2H, m), 7.643-7.697 (2H, m), 7.878 (1H, s), 8.379 (1H, s), 8.398 (1H, d, *J* = 2.3 Hz), 10.700 (1H, s); HRMS (ESI): m/z [M] calcd. For $C_{13}H_{10}N_4O$: 238.0332; found: 238.0277.

4-(5-((2-(phthalazin-1-yl)hydrazono)methyl)furan-2-yl)benzoic acid (5b):

Yield: 87 %; MF: $C_{20}H_{14}N_4O_3$; Mol.Wt.: 358.35; Colour: Yellow; MP: 278ºC.
IR (cm^{-1}): 3225.82, 1689.86, 2835.17, 1608.10, 1530.44, 1383.64,1227.96, 1173.27, 875.62;^{1}H NMR(400 MH_z, $CDCl_3$) δ: 6.531 (d, 1H, 3.2 Hz), 6.795 (d, 1H, 3.2 Hz), 7.514-7.566 (m, 2H), 7.643-7.697 (m, 2H), 7.878 (s, 1H), 8.379 (s, 1H), 8.398 (d, 1H, 2.3 Hz), 10.700 (s, 1H)

1-(2-((5-(4-nitrophenyl)furan-2-yl)methylene)hydrazinyl)phthalazine (5c):

Yield: 91%; MF: $C_{19}H_{13}N_5O_3$; Mol.Wt.: 359.34; Colour: Crimson red; MP: 291^{o}C.
IR (cm^{-1}): 3287.07, 3108.73, 1592.81, 1567.59 & 1323.32, 1243.16, 1182.93, 862.75; ^{1}H NMR(400 MH_z, $CDCl_3$) δ: 6.531 (d, 1H, 3.2 Hz), 6.795 (d, 1H, 3.2 Hz), 7.514-7.566 (m, 2H),7.643-7.697 (m, 2H), 7.878 (s, 1H), 8.379 (s, 1H), 8.398 (d, 1H, 2.3 Hz), 10.700 (s, 1H).

1-(2-((5-(3,4-dichlorophenyl)furan-2-yl)methylene)hydrazinyl)phthalazine (5d):

Yield: 90%; MF: $C_{19}H_{12}Cl_2N_4O$; Mol.Wt.: 383.23; Colour: Yellow solid; MP: 208°C.

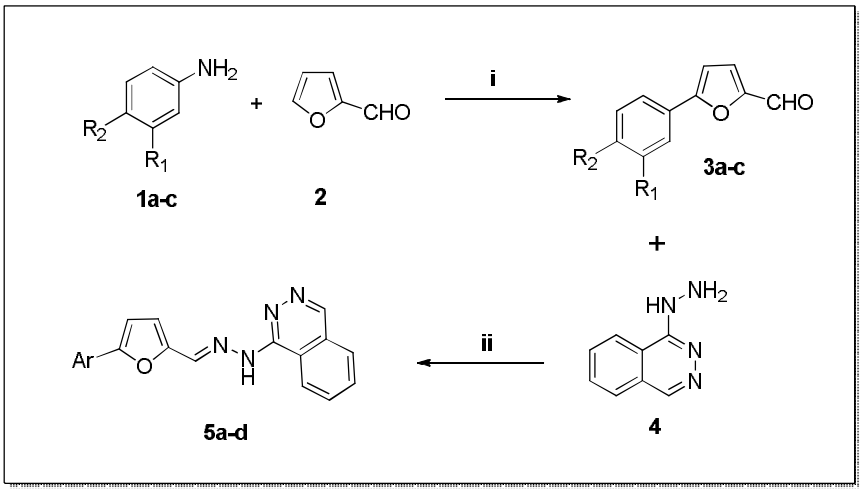
IR (cm^{-1}): 3287.07, 3108.73, 1592.81, 1567.59 & 1323.32, 1243.16, 1182.93, 862.75; ^{1}H NMR(400 MH_z, $CDCl_3$) δ: 6.811 (1H, d, *J* = 3.6 Hz), 6.879 (1H, d, *J* = 3.6 Hz), 7.498 (1H, d, *J* = 8.4 Hz), 7.548-7.570 (1H, m), 7.604-7.630 (1H, dd, J_1 = 2 Hz & J_2 = 8.4 Hz), 7.675-7.716 (2H, m), 7.875 (1H, d, *J* = 2.8 Hz), 7.923 (1H, s), 8.379 (1H, s), 8.422 (1H, d, *J* = 2.8 Hz), 10.753 (1H, s); ^{13}C NMR (100 MH_z, $CDCl_3$) δ: 108.82, 115.40, 123.42, 124.31, 125.91, 126.18, 130.01, 130.80, 131.80, 133.16, 142.87, 151.18, 153.24; HRMS (ESI): m/z [M] calcd. For $C_{19}H_{12}Cl_2N_4O$: 383.2311; found: 383.2306.

4. RESULT AND DISCUSSION:

4.1 CHEMISTRY:

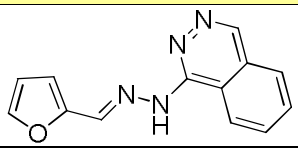
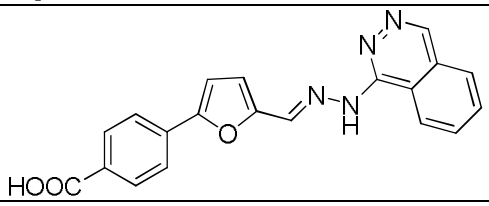
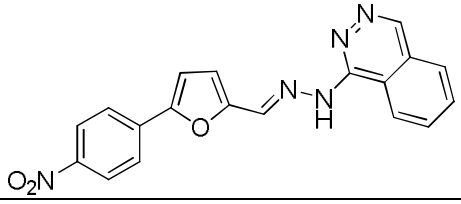
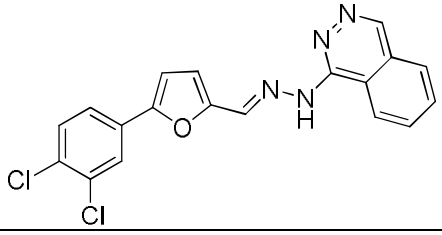
In the present investigation, the 5-aryl furan-2-carbaldehyde was synthesized through Meerwein arylation [22 -25], in which the substituted anilines after diazotisation using HCl and $NaNO_2$. The diazonnium salt when treated with the furan-2-carbaldehyde in presence of $CuCl_2$ as catalyst in aqueous media on stirring at room temperature gave 5-aryl furan-2-carbaldehyde. This intermediate was confirmed by TLC and characterized by IR, ^{1}H NMR and Mass Spectroscopy.

The title compounds were synthesized from equimolar amount of substituted 5-aryl furan-2-carbaldehydes and on reaction with phthalazinyl hydrazine in presence of catalytic amount of glacial acetic acid in ethanol at reflux condition. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectroscopy.



Reagents and conditions: (i) Conc. HCl, 0 °C, $NaNO_2$/H2O, $CuCl_2$, stirr at rt, 4-6 h;
(ii) Glacial acetic acid, ethanol, 70-80 °C, 4-6 h.

Table 1: Synthesized phthalazinyl hydrazones of furan-2-carbaldehyde (5a-d)

Sr. No.	Entry	Product	MP °C	Yield %
1	**5a**		176	89
2	**5b**		278	87
3	**5c**		291	91
4	**5d**		208	90

The IR spectrum of substituted phthalazinyl hydrazones of furan-2-carbaldehyde showed that, the weak absorption band observed at ~ 3000-3300 cm^{-1} is due to N–H stretch and absorption band at ~2800-3000 cm^{-1} is for C– H stretch of hydrazone moiety. The absorption band at ~ 1580-1600 cm^{-1} due to >C=N– stretch. The absorption band at ~ 1230-1250 cm^{-1} is observed due to the N–N stretch and C–O–C ether stretch gives the absorption band at ~ 1170-1190 $cm.^{-1}$ ^1H NMR spectra of (taken in 400 MHz in $CDCl_3$) phthalazinyl hydrazones of furan-2-carbaldehyde reveals that, the two aromatic protons of furan shown doublet each at ~ 6.53-6.90 ppm and ~ 6.79-6.90 ppm. The singlet at δ ~ 7.87-7.92 ppm is due to the hydrogen attached to the carbon of hydrazone, whereas the specific singlet at δ ~ 8.37-8.38 ppm is due one of the hydrogen of phthalazine and the sharp, characteristic singlet at δ ~ 10.70-10.75 ppm is due to the hydrogen attached to nitrogen (>N–H). The remaining aromatic protons resonated at δ ~ 7.49-7.87 ppm. The mass spectra of corresponding substituted phthalazinyl hydrazones of furan-2-carbaldehyde confirm their molecular formula and molecular weight.

5. CONCLUSION:

We have efficiently designed and synthesized four phthalazinyl hydrazones of furan-2-carbaldehyde from differently substituted furan-2-carbaldehyde and phthalazinyl hydrazine with excellent yields without formation of any side products. The synthesized phthalazinyl hydrazones would lead the promising pharmacological properties in the future.

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