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Synthesis, characterization and biological study of some new N-acetyl pyrazole derivatives

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A series of *N*-acetyl pyrazole derivatives, 1-acetyl-3-aryl-5-[5'-(4-nitrophenyl)-2'-furyl]-4,5-dihydro-1*H*-pyrazoles **(5a-j)** were synthesized by cyclocondensation reaction between 1-aryl-3-[5-(4-nitrophenyl)-2-furyl]prop-2-en-1-ones **(4a-j)** and hydrazine hydrate in glacial acetic acid at reflux temperature. Before that, compounds **(4a-j)** were synthesized by the condensation of 5-(4-nitrophenyl) furan-2-carbaldehyde **(3)** with various aromatic ketones by using alkali as catalyst. The constitution of the synthesized products has been characterized by using elemental analysis, Infrared,^{1}H-NMR, ^{13}C-NMR spectroscopy and further supported by Mass spectroscopy. All the products have been screened for their *in-vitro* biological assay like antibacterial activity towards *Gram-positive* and *Gram-negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml. It was exposed that the compounds **5a**, **5b**, **5c**, **5d**, **5g, 5h** and **5j** showed motivating antibacterial and antifungal activity compared to the used reference standard.

1. Introduction

Pyrazoles are one of the most considered groups of compounds among the azole family. Indeed, a massive diversity of synthesis methods and synthetic similarities have been reported over the past years.[1] The presence of the pyrazole nucleus in different structures leads to expanded applications in different areas such as technology, medicine, pigments and agriculture.[2] Many pyrazole derivatives has found their applications as nonsteroidal anti-inflammatory drugs clinically, such as anti-pyrine or phenazone (analgesic and antipyretic), metamizole or dipyrone (analgesic and antipyretic), aminopyrine or aminophenazone (anti-inflammatory, antipyretic, and analgesic), phenylbutazone (anti-inflammatory, antipyretic mainly used in osteoarthritis, rheumatoid arthritis, spondylitis, Reiter's disease), sulfinpyrazone (chronic gout), and oxyphenbutazone (antipyretic, analgesic, anti-inflammatory, mild uricosuric).[3] In actual, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant, antimalarial as well as antiviral agents.[4-17] Nowadays, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. Also, this heterocycle can be traced in a number of well-established drugs like Celecoxib(anti-inflammatory), Lonazolac(anti-inflammatory), Fezolamine (anti-depressent), Difenamizole(analgesic), Rimonabant (anti-obesity) belonging to different categories with diverse therapeutic activities.[18-22]

An abundant synthetic method to substituted pyrazoles has been released during the past two decades.[23] These methods included the construction of two C-N bonds via condensation of 1,3-dicarbonylcompounds or ynones with hydrazine,[24] simultaneous formation of one C-N bond and one C-C bond via [3+2] cycloaddition of 1,3-dipoles, i.e., hydrazones or α-diazo compounds with alkynes or alkenes-bearing electron-withdrawing groups. In addition, the direct N-N bond formation to install into multi substituted pyrazoles from nitriles via metal-imido intermediates was also available.[25] An example of forming one C-N bond via intramolecular cyclization of vinyl-diazoacetates was discovered recently.[26]

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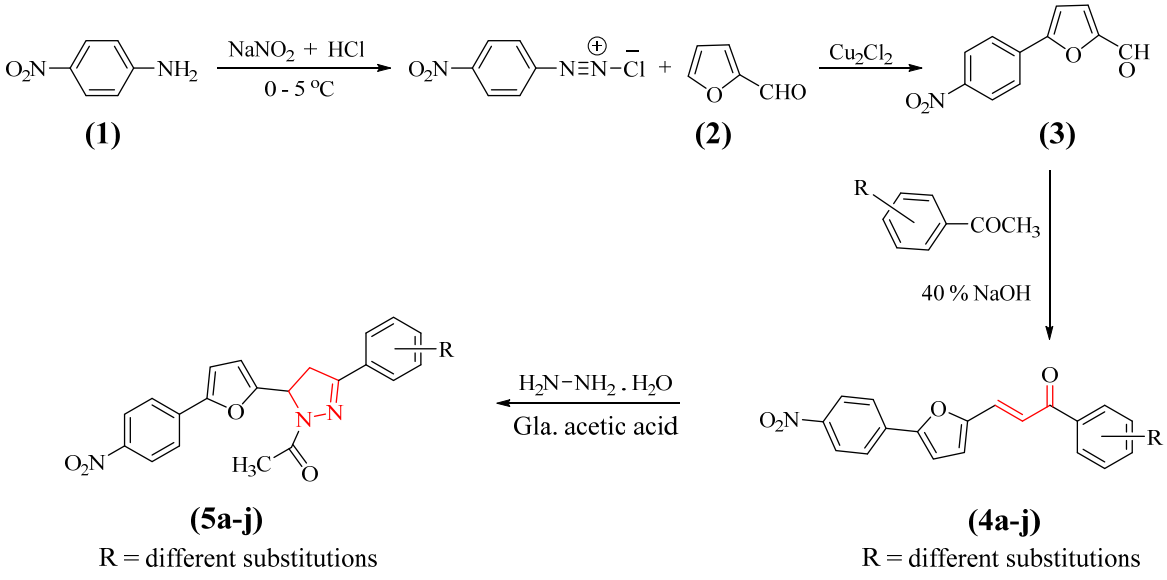
From several processes of synthesis of pyrazoles, the most dominant is [3+2] cycloaddition process (32CA).[27] Reaction permits obtaining pyrazoles with "full atomic economy" and preservation of primary conformation of substrates. Most of the synthesis reactions of pyrazoles in a course of [3+2] cycloaddition is grasped under mild and non-catalyst condition giving high yields.[28,29] These conditions approach one of the main values of green chemistry.

Taking these considerations into account, herein is reported the synthesis of some 1-acetyl-3-aryl-5-[5'-(4-nitrophenyl)-2'-furyl]-4,5-dihydro-1*H*-pyrazoles **(5a-j)** to study their bipotentiality.

2. Results and Discussion

2.1 Chemistry and Spectroscopic discussion

The target compounds 1-acetyl-3-aryl-5-[5'-(4-nitrophenyl)-2'-furyl]-4,5-dihydro-1*H*-pyrazoles **(5a-j)** were synthesized as charted in Reaction **Scheme-1**. The title compounds, 1-acetyl-3-aryl-5-[5'-(4-nitrophenyl)-2'-furyl]-4,5-dihydro-1*H*-pyrazoles **(5a-j)** were synthesized by a four-step procedure starting from 4-nitro aniline **(1)**. Diazotization reaction of 4-nitroaniline **(1)** (0.01mole) in dil. HCl (15%) and water (90 ml) with $NaNO_2$ solution (30%) at 0-5 °C followed by coupling with freshly distilled furfural **(2)** (0.1 mole) in presence of aqueous cupric chloride (2.5 g in 10 ml of water) gives 5-(4-nitrophenyl) furan-2-carbaldehyde **(3)**. The condensation rection of 5-(4-nitrophenyl) furan-2-carbaldehyde **(3)** with various aromatic ketones in methanol + DMF (15+5 ml) solvent in presence of 40% NaOH (1 ml) afforded 1-aryl-3-[5-(4-nitrophenyl)-2-furyl]prop-2-en-1-ones **(4a-j)**. Cyclocondensation reaction of **(4a-j)** and hydrazine hydrate in glacial acetic acid at reflux temperature gives 1-acetyl-3-aryl-5-[5'-(4-nitrophenyl)-2'-furyl]-4,5-dihydro-1*H*-pyrazoles **(5a-j)**.



(Scheme-I)

The purity of all compounds is checked by thin layer chromatography and their characterization is carried out by means of elemental analysis, Infrared, ^{1}H-NMR, ^{13}C-NMR spectroscopy and further supported by Mass spectroscopy. Among all, the IR spectrum of compound **5e** showed strong bands at 1654 cm^{-1} which are due to carbonyl stretching of –$COCH_3$ group. The compound showed bands at 2942 cm^{-1} and 3063 cm^{-1} which are due to aliphatic C–H stretching and aromatic C–H stretching vibration respectively. The band observed at 1614 cm^{-1} and 1175 cm^{-1} is due to aromatic C=N and C–N stretching vibration of pyrazoline ring respectively. Band of C–H out of plane bending for disubstituted aromatic ring is observed at 852 cm^{-1}. Two bands at 1494 cm^{-1} and 1295 cm^{-1} are observed due to N=O asymmetric and symmetric stretching vibrations respectively. The band observed at 1256 cm^{-1} and 1043 cm^{-1} is due to C–O–C asymmetric and symmetric stretching of furyl moiety respectively. The mass spectrum of compound **5f** showed M^+ peak at 389 m/z. The ^{1}H-NMR spectrum of compound **5e** (in $CDCl_3$) showed singlet signal at 3.87 δ due to –OCH_3 group. The singlet signal at 2.41 δ due to the –$COCH_3$ group present in pyrazoline ring. The two doublet of doublet at 3.51 δ (*J=4.96 & 17.44 Hz*) and at 3.69 δ (*J=11.72 & 17.44 Hz*) is due to diasteriotropic protons (CH_2) of pyrazoline ring. A doublet of doublet at 5.75 δ (*J=4.92 & 11.72 Hz*) integrating for one proton is due to chiral C–H of pyrazoline ring. The remaining ten aromatic protons of furyl moiety and phenyl ring appeared between 6.47 δ to 8.20 δ. The ^{13}C-NMR spectrum of compound **5e** showed signals at 168.52, 162.95, 154.73, 152.68, 151.70, 150.07, 147.93, 136.43, 128.75, 126.24, 124.47, 114.41, 105.23, 101.02, 55.84, 51.64, 38.12 and 22.84 corresponding to twenty-two different type of carbon atoms present in the compounds. The most downfield signal appeared at 168.52 δ can be assigned to the carbonyl carbon of –$NCOCH_3$ group in pyrazoline nucleus. The signals appeared at 22.84 δ and 55.84 δ can be assigned to methyl carbon of –$NCOCH_3$ and –OCH_3 respectively. The signal of two aliphatic carbon

of pyrazoline ring appeared at 38.12 δ and 51.64 δ. The rest of signals are corresponding to alkene and aromatic carbons of furyl and phenyl nucleus.

All synthesized compounds were screened for their *in-vitro* biological assay like antibacterial activity towards *Gram-positive* and *Gram-negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg/ml.

2.2 biological activity

All the synthesized compounds have been evaluated for antimicrobial activity.

Antibacterial activity

The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hr. old subcultures of *Bacillus coccus*, *Staphylococcus aureus*, *Aerogenes*, *Pseudomonas aeruginosa* in separate conical flasks at 40-50 ºC and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spreaded in a Petri dish (13 cm diameter) and allowed to set for 2 hr. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40 µg) solution of sample in DMF. The plates were incubated at 37 ºC for 24 hrs. and the control was also maintained with 0.04 ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in *millimeter* and recorded in **Table 1**.

Antifungal activity

Aspergillus niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on *subouraud's agar slants*. Sterilized *sabouraud's agar* medium was inoculated with 72 hrs. old 0.5 ml suspension of fungal spores in a separate flask.

About 25 ml of inoculated medium was evenly spreaded in a Petri dish and allowed to set for two hrs. The plates were incubated at 30 ºC for 48 hrs. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in *mm* was measured. Along the test solution in each Petri dish one cup was filled with solvent which act as control. Standard drugs like *Amoxicillin*, *Benzyl Penicillin*, *Ciprofloxacin*, *Erythromycin* and *Griseofulvin* were used for comparison purpose. The zones of inhibition are recorded in **Table 1**.

Table 1. Antimicrobial screening results of compounds **5a-j**

Sample ID	R	Zone of inhibition in *mm*				
		Antibacterial activity (%)				Antifungal activity (%)
		B. coccus	*S. aureus*	*Aerogenes*	*Pseudomonas*	*A. niger*
5a	H	22	9	19	20	20
5b	4-Cl	17	22	21	18	24
5c	2-NO_2	20	16	14	22	15
5d	4-NO_2	18	20	19	23	17
5e	4-OCH_3	20	17	15	18	13
5f	4-CH_3	18	19	13	20	22
5g	4-F	10	9	23	20	14
5h	4-Br	24	12	18	18	20
5i	2-OH	16	21	21	14	19
5j	4-OH	19	23	16	15	15
Amoxicillin	-	25	25	20	22	00
Benzyl penicillin	-	18	19	21	21	00
Ciprofloxacin	-	20	15	22	16	00
Erythromycin	-	22	21	19	23	00
Greseofulvin	-	00	00	00	00	26

From activity data, it is observed that compounds **5a** and **5h** were found to be active which is attributed to the presence of simple and 4-Br-substituted benzene ring at C_3-position of pyrazole nucleus, while compounds **5c**, **5d**, **5e**, **5f** and **5j** show moderate activity against *Bacillus coccus* with reference to standard drugs. Compounds **5b** and **5j** were found to be active due to the presence of 4-Cl and 4-OH substituted benzene ring at C_3-position of pyrazole nucleus, while compounds **5d, 5f** and **5i** show moderate activity against *Staphylococcus aureus.* Against *Aerogenes* strain, compound **5b, 5g** and **5i** were found to be active which is attributed to the presence of 4-Cl, 4-F and 2-OH substituted benzene ring at C_3-position of

pyrazole nucleus, while compounds **5a**, **5d** and **5h** were found to be moderate active. Against *Pseudomonas aeruginosa,* compounds **5c** and **5d** are highly active due to the presence of 2-NO_2 and 4-NO_2 substituted benzene ring at C_3-position of pyrazole nucleus than others. Compounds **5b** were highly active because of presence of 4-Cl substituted benzene ring at C_3-position of pyrazole nucleus while compounds **5a**, **5f** and **5h** show moderate activity against *Aspergillus niger* as compare to standard drugs.

Among *N*-acetyl pyrazole derivatives, it was interesting to notice that the activity depends on the substituents rather than the basic skeleton of the molecule. It was noticed that, electron donating groups -Cl, -F, -Br and -OH on the benzene ring at C_3-position of pyrazole nucleus, enhanced their antimicrobial activity and are better antimicrobial agents, while due to the presence of strong electron withdrawing substituents on the aromatic ring to the pyrazole nucleus decreases the antimicrobial activity.

Overall, it was found that donating part in the aromatic structure impacts the synthesized molecules effectiveness.[30,31]

3. Conclusions

In summary, a series of 1-acetyl-3-aryl-5-[5'-(4-nitrophenyl)-2'-furyl]-4,5-dihydro-1*H*-pyrazoles **(5a-j)** were synthesized and evaluated as anti-microbial agents against a group of antibacterial and antifungal strains. They were found to possess reasonably good antifungal activity and compounds **5a, 5b, 5c, 5d, 5g, 5h** and **5j** were found to be the most potent anti-microbial agents. It will be the topic of new research to substitute it with greener reagents and solvents, finding more effective anti-microbial agents.

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4. Experimental

4.1. Materials and Methods

Chemicals and solvents were purchased from Sigma-Aldrich Chemical Co., Merck chemical, Finar, and Spectrochem Ltd. Thin layer chromatography [silica gel G (E Merck) plates] was used to monitor the reactions and purity of newly synthesized compounds. Visualization was achieved with UV light (254 and 365 nm) or with iodine vapor. The melting point were determined by electrothermal apparatus using open capillary tubes and are uncorrected. IR spectra were recorded on a Shimadzu 8400 FTIR instrument in KBr disc and only significant absorbance levels (cm^{-1}) are listed. ^{1}H (400 MHz) and ^{13}C (101 MHz) NMR spectra were recorded on a "Bruker AVANCE III spectrometer" in $CDCl_3$/ DMSO-d_6 solvent using TMS as internal standard. Chemical shift is given in δ ppm. Mass spectra were determined using direct inlet probe on GCMS-QP2010 mass spectrometer (Shimadzu, Kyoto, Japan). Elemental analysis was performed on a Carlo Erba EA1108 elemental analyser.

4.2. General procedure

4.2.1 Procedure for the synthesis of 5-(4-nitrophenyl) furan-2-carbaldehyde **(3)**

A mixture of 4-nitroaniline **(1)** (13.8 g, 0.01 mole), dil. HCl (15%, 60 ml) and water (90 ml) was heated to get a clear solution. The solution was cooled to 0 °C and diazotized with $NaNO_2$ solution (30%, 24 ml) and freshly distilled furfural **(2)** (11.1 ml, 0.1 mole) and aqueous cupric chloride (2.5 g in 10 ml of water) were added with stirring. The stirring was continued for 5 hrs. The separated solid was collected by filtration and washed with cold methanol, crystallized from a mixture of ethanol-DMF (3:7 ratio). Yield 70%, m.p. 187 ^{O}C. IR(KBr): 3052 (C=C-H str.), 2745 and 2830 (C-H str. of aldehyde), 1729 (C=O str. of aldehyde), 1510 (N=O str. asym.), 1490 (C=C str.), 1354 (N=O str. asym.), 1250 (C-O-C str.sym.), 1059 (C-O-C str. asym.) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, J = 3.62 Hz, 1H, Furyl-H_e), 7.69 (d, J = 3.69 Hz, 1H, Furyl-H_f), 7.91 (d, J = 8.19 Hz, 2H, Ar-$H_{b,b'}$), 8.33 (d, J = 9.12 Hz, 2H, Ar-$H_{a,a'}$), 9.72 (s, 1H, -CHO); ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 178.11, 159.46, 152.33, 136.40, 147.93, 124.46, 116.20, 109.83; EI-MS: m/z 217. ($C_{11}H_7NO_4$; required: C, 60.83; H, 3.25; N, 6.45%; found: C, 60.79; H, 3.21; N, 6.39%).

4.2.2 Procedure for the synthesis of 1-aryl-3-[5-(4-nitrophenyl)furan-2-yl]prop-2-en-1-ones **(4a-j)**

A solution of substituted acetophenone (0.01 mole) in minimum quantity of methanol (10 ml) was added to a mixture of 5-(4-nitrophenyl) furan-2-carbaldehyde **(3)** (2.17 gm, 0.01 mole) in methanol + DMF (15+5 ml) and 40% NaOH (1 ml) was added to make it alkaline. The reaction mixture was then stirred for 20-24 hrs at room temperature. The product was isolated by filtration and crystallized from suitable solvent to give pure products.

Spectral data of 1-(4-methoxyphenyl)-3-[5-(4-nitrophenyl)furan-2-yl]prop-2-en-1-one **(4e)**

Yield 62%; m.p. 120-22°C; IR (KBr): 3055 (C=C-H str.), 1649 (C=O str.), 1517 (C=C), 1250 (C-O-C str.sym.), 1059 (C-O-C str. asym.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 3.91 (s, 3H, Ar-OCH_3), 6.84 (d, J = 3.64 Hz, 1H, Furyl-H_e), 6.99 (d, J = 3.90 Hz, 1H, Furyl-H_f), 7.02 (d, J = 8.84 Hz, 2H, Ar-$H_{d,d'}$), 7.60 (d, 2H, vinyl-H_A, H_B), 7.91 (d, J = 8.92 Hz, 2H, Ar-$H_{b,b'}$), 8.09 (d, J = 8.84 Hz, 2H, Ar-$H_{c,c'}$), 8.31 (d, J = 9.20 Hz, 2H, Ar-$H_{a,a'}$); ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 189.72, 166.45, 156.07, 150.52, 147.91, 136.40, 130.30, 127.32, 124.47, 120.95, 114.83, 106.43, 109.96, 55.84; EI-MS: m/z 349. Anal. Calcd. for $C_{20}H_{15}NO_5$; required: C, 68.76; H, 4.33; N, 4.01%; found: C, 68.71; H, 4.29; N, 3.96%).

4.2.3 Procedure for the synthesis of 1-acetyl-3-aryl-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazoles **(5a-j)**

A mixture of 1-aryl-3-[5-(4-nitrophenyl)-2-furyl]prop-2-en-1-one **(4a-j)** (0.01 mole) and hydrazine hydrate (0.04 mole) in acetic acid (25 ml) was refluxed in oil-bath for 10-13 hrs. The solution was poured on crushed ice. The products were isolated by filtration and crystallized from suitable solvent to give analytically pure products.

4.3 Physical and Spectral Data

4.3.1 1-acetyl-3-phenyl-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5a)

Yield 58%; m.p. 112-114°C; IR (KBr): 3050 (C=C-H str.), 1668 (C=O str.), 1614 (C=N str.), 1452 (C=C str.), 1160 (C-N str.), 1243 (C-O-C str.sym.), 1103 (C-O-C str. asym.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.39 (s, 3H, -$COCH_3$), 3.47 (dd, 1H, Pyrazole-H_A), 3.81 (dd, 1H, Pyrazole-H_B), 5.64 (dd, J = 4.72 & 10.96 Hz, 1H, Pyrazole-H_C), 6.52 (d, J = 3.49 Hz, 1H, Furyl-H_d), 6.87 (d, J = 3.58 Hz, 1H, Furyl-H_e), 6.88-7.74 (m, 5H, Ar-H); 7.64 (d, J = 8.97 Hz, 2H, Ar-$H_{c,c'}$), 8.27 (d, J = 9.07 Hz, 2H, Ar-$H_{d,d'}$); ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.54, 152.42, 151.70, 150.03, 147.95, 136.40, 131.03, 128.50, 126.31, 124.50, 105.24, 101.04, 51.62, 38.14, 22.82; EI-MS: m/z 375. Anal. Calcd. for $C_{21}H_{17}N_3O_4$; required: C, 67.23; H, 4.56; N, 11.19%; found: C, 67.19; H, 4.53; N, 11.16%).

4.3.2 1-acetyl-3-(4-chlorophenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5b)

Yield 52%; m.p. 128-130°C; IR (KBr): 3042 (C=C-H str.), 1680 (C=O str.), 1610 (C=N str.), 1430 (C=C str.), 1165 (C-N str.), 1235(C-O-C str.sym.), 1090 (C-O-C str. asym.), 570 (C-Cl str.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.44 (s, 3H, -$COCH_3$), 3.51 (dd, 1H, Pyrazole-H_A), 3.63 (dd, 1H, Pyrazole-H_B), 5.71 (dd, J = 4.78 & 10.82 Hz, 1H, Pyrazole-H_C), 6.42 (d, J = 3.56 Hz, 1H, Furyl-H_d), 6.87 (d, J = 3.52 Hz, 1H, Furyl-H_e), 7.12 (d, J = 8.56 Hz, 2H, Ar-$H_{a,a'}$); 7.65 (d, J = 9.07 Hz, 2H, Ar-$H_{b,b'}$), 7.74 (d, J = 8.90 Hz, 2H, Ar-$H_{c,c'}$), 8.12 (d, J = 8.87 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.51, 152.28, 151.68, 150.03, 147.92, 136.50, 134.52, 128.36, 126.28, 124.53, 105.22, 101.01, 51.60, 38.11, 22.82; EI-MS: m/z 410. Anal. Calcd. for $C_{21}H_{16}ClN_3O_4$; required: C, 61.49; H, 3.93; N, 10.25%; found: C, 61.45; H, 3.89; N, 10.19%).

4.3.3 1-acetyl-3-(2-nitrophenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5c)

Yield 66%; m.p. 134-136°C; IR (KBr): 3039 (C=C-H str.), 1665 (C=O str.), 1608 (C=N str.), 1457 (C=C str.), 1147 (C-N str.), 1232 (C-O-C str.sym.), 1080 (C-O-C str. asym.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.44 (s, 3H, -$COCH_3$), 3.51 (dd, 1H, Pyrazole-H_A), 3.63 (dd, 1H, Pyrazole-H_B), 5.71 (dd, J = 4.78 & 10.82 Hz, 1H, Pyrazole-H_C), 6.42 (d, J = 3.56 Hz, 1H, Furyl-H_d), 6.87 (d, J = 3.52 Hz, 1H, Furyl-H_e), 7.12-7.65 (m, 4H, Ar-H), 7.74 (d, J = 8.90 Hz, 2H, Ar-$H_{c,c'}$), 8.12 (d, J = 8.87 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.53, 152.56, 151.69, 150.01, 147.93, 136.43, 135.42, 134.32, 131.87, 126.41, 125.43, 124.47, 105.23, 101.02, 51.63, 37.13, 22.81; EI-MS: m/z 420. Anal. Calcd. for $C_{21}H_{16}N_4O_5$; required: C, 60.04; H, 3.87; N, 13.33%; found: C, 60.01; H, 3.82; N, 13.29%).

4.3.4 1-acetyl-3-(4-nitrophenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5d)

Yield 64%; m.p. 126-128°C; IR (KBr): 3042 (C=C-H str.), 1669 (C=O str.), 1618 (C=N str.), 1462 (C=C str.), 1132 (C-N str.), 1240 (C-O-C str.sym.), 1090 (C-O-C str. asym.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.48 (s, 3H, -$COCH_3$), 3.53(dd, 1H, Pyrazole-H_A), 3.60 (dd, 1H, Pyrazole-H_B), 5.68 (dd, J = 4.56 & 10.67 Hz, 1H, Pyrazole-H_C), 6.47 (d, J = 3.41 Hz, 1H, Furyl-H_d), 6.81 (d, J = 3.52 Hz, 1H, Furyl-H_e), 6.87 (d, J = 8.46 Hz, 2H, Ar-$H_{a,a'}$); 7.45(d, J = 8.87 Hz, 2H, Ar-$H_{b,b'}$), 7.82 (d, J = 9.04 Hz, 2H, Ar-$H_{c,c'}$), 8.09 (d, J = 8.77 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.54, 152.32,

151.70, 150.03, 147.90, 142.53, 136.45, 127.74, 126.49, 124.40, 105.21, 101.04, 51.63, 38.10, 22.81; EI-MS: m/z 420. Anal. Calcd. for $C_{21}H_{16}N_4O_5$; required: C, 60.04; H, 3.87; N, 13.33%; found: C, 60.03; H, 3.83; N, 13.28%).

4.3.5 1-acetyl-3-(4-methoxylphenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5e)

Yield 71%; m.p. 102-104°C; IR (KBr): 3063 (C=C-H str.), 1654 (C=O str.), 1614 (C=N str.), 1458 (C=C str.), 1175 (C-N str.), 1250 (C-O-C str.sym.), 1059 (C-O-C str. asym.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.41 (s, 3H, -$COCH_3$), 3.87 (s, 3H, Ar-OCH_3), 3.51 (dd, 1H, Pyrazole-H_A), 3.69 (dd, 1H, Pyrazole-H_B), 5.75 (dd, J = 4.92 & 11.72 Hz, 1H, Pyrazole-H_C), 6.47 (d, J = 3.44 Hz, 1H, Furyl-H_d), 6.81 (d, J = 3.48 Hz, 1H, Furyl-H_e), 6.98 (d, J = 8.96 Hz, 2H, Ar-$H_{a,a'}$); 7.69 (d, J = 9.00 Hz, 2H, Ar-$H_{b,b'}$), 7.74 (d, J = 8.92 Hz, 2H, Ar-$H_{c,c'}$), 8.20 (d, J = 9.00 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.52, 162.95, 154.73, 152.68, 151.70, 150.07, 147.93, 136.43, 128.75, 126.24, 124.47, 114.41, 105.23, 101.02, 55.84, 51.64, 38.12, 22.84; EI-MS: m/z 405. Anal. Calcd. for $C_{22}H_{19}N_3O_5$; required: C, 65.23; H, 4.70; N, 10.36%; found: C, 68.19; H, 4.69; N, 10.32%).

4.3.6 1-acetyl-3-(4-methylphenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5f)

Yield 59%; m.p. 118-120°C; IR (KBr): 3046 (C=C-H str.), 2832 (alkane C-H str. Sym.), 1647 (C=O str.), 1607 (C=N str.), 1442 (C=C str.), 1162 (C-N str.), 1220 (C-O-C str.sym.), 1070 (C-O-C str. asym.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.49 (s, 3H, -$COCH_3$), 2.28 (s, 3H, Ar-CH_3), 3.47 (dd, 1H, Pyrazole-H_A), 3.42 (dd, 1H, Pyrazole-H_B), 5.82 (dd, J = 4.78 & 11.32 Hz, 1H, Pyrazole-H_C), 6.62 (d, J = 3.54 Hz, 1H, Furyl-H_d), 6.89 (d, J = 3.58 Hz, 1H, Furyl-H_e), 6.88 (d, J = 8.92 Hz, 2H, Ar-$H_{a,a'}$), 7.63 (d, J = 8.75 Hz, 2H, Ar-$H_{b,b'}$), 7.71 (d, J = 8.89 Hz, 2H, Ar-$H_{c,c'}$), 8.22 (d, J = 9.04 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.50, 152.41, 151.66, 150.05, 147.90, 140.75, 136.41, 133.45, 129.15, 127.06, 126.23, 124.49, 105.20, 101.05, 51.60, 38.11, 22.82, 21.33; EI-MS: m/z 389. Anal. Calcd. for $C_{22}H_{19}N_3O_5$; required: C, 67.89; H, 4.88; N, 10.79%; found: C, 67.86; H, 4.81; N, 10.74%).

4.3.7 1-acetyl-3-(4-fluorolphenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5g)

Yield 52%; m.p. 144-146°C; IR (KBr): 3052 (C=C-H str.), 1662 (C=O str.), 1607 (C=N str.), 1440 (C=C str.), 1143 (C-N str.), 1214 (C-O-C str.sym.), 1047 (C-O-C str. asym.), 1329 (C-F str.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): ^1H NMR (400 MHz, $CDCl_3$): 1.98 (s, 3H, -$COCH_3$), 3.87 (dd, 1H, Pyrazole-H_A), 3.67 (dd, 1H, Pyrazole-H_B), 5.31 (dd, J = 4.82 & 10.71 Hz, 1H, Pyrazole-H_C), 6.39 (d, J = 3.45 Hz, 1H, Furyl-H_d), 6.91 (d, J = 3.38 Hz, 1H, Furyl-H_e), 7.26 (d, J = 8.36 Hz, 2H, Ar-$H_{a,a'}$); 7.69 (d, J = 8.89 Hz, 2H, Ar-$H_{b,b'}$), 7.72 (d, J = 9.02 Hz, 2H, Ar-$H_{c,c'}$), 8.27 (d, J = 8.81 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.50, 165.23, 152.47, 151.69, 150.03, 147.90, 136.43, 132.05, 129.52, 126.18, 124.46, 115.65, 105.22, 101.03, 51.63, 38.10, 22.83; EI-MS: m/z 393. Anal. Calcd. for $C_{21}H_{16}FN_3O_4$; required: C, 64.14; H, 4.08; N, 10.68%; found: C, 64.11; H, 4.05; N, 10.63%).

4.3.8 1-acetyl-3-(4-bromolphenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5h)

Yield 63%; m.p. 138-140°C; IR (KBr): 3041 (C=C-H str.), 1660 (C=O str.), 1610 (C=N str.), 1449 (C=C str.), 1150 (C-N str.), 1210 (C-O-C str.sym.), 1045 (C-O-C str. asym.), 620 (C-Br str.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): ^1H NMR (400 MHz, $CDCl_3$): 1.96 (s, 3H, -$COCH_3$), 3.85 (dd, 1H, Pyrazole-H_A), 3.69 (dd, 1H, Pyrazole-H_B), 5.34 (dd, J = 4.80 & 10.73 Hz, 1H, Pyrazole-H_C), 6.34 (d, J = 3.42 Hz, 1H, Furyl-H_d), 6.93 (d, J = 3.37 Hz, 1H, Furyl-H_e), 7.59 (d, J = 8.31 Hz, 2H, Ar-$H_{a,a'}$); 7.72 (d, J = 8.89 Hz, 2H, Ar-$H_{b,b'}$), 7.77 (d, J = 9.03 Hz, 2H, Ar-$H_{c,c'}$), 8.26 (d, J = 8.82 Hz, 2H, Ar-$H_{d,d'}$), ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.51, 152.32, 151.68, 150.06, 147.93, 136.40, 135.45, 131.72, 128.65, 126.20, 125.40, 124.47, 105.20, 101.06, 51.62, 38.13, 22.82; EI-MS: m/z 454. Anal. Calcd. for $C_{21}H_{16}BrN_3O_4$; required: C, 55.50; H, 3.52; N, 9.25%; found: C, 55.47; H, 3.49; N, 9.21%).

4.3.9 1-acetyl-3-(2-hydroxylphenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5i)

Yield 57%; m.p. 162-164°C; IR (KBr): 3540 (O-H str.), 3050 (C=C-H str.), 1668 (C=O str.), 1620 (C=N str.), 1447 (C=C str.), 1141 (C-N str.), 1247 (C-O-C str.sym.), 1040 (C-O-C str. asym.), 1127 (C-OH str.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.06 (s, 3H, -$COCH_3$), 3.59 (dd, 1H, Pyrazole-H_A), 3.89 (dd, 1H, Pyrazole-H_B), 5.17 (dd, J = 4.90 & 11.07 Hz, 1H, Pyrazole-H_C), 6.37 (d, J = 3.47 Hz, 1H, Furyl-H_d), 6.87 (d, J = 3.58 Hz, 1H, Furyl-H_e), 6.90 - 7.62 (m, 4H, Ar-H), 7.74 (d, J = 8.97 Hz, 2H, Ar-$H_{c,c'}$), 8.30 (d, J = 9.04 Hz, 2H, Ar-$H_{d,d'}$), 12.98 (s, 1H, -OH); ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.50, 162.54, 152.43, 151.68, 150.07, 147.94, 136.42, 132.42, 141.43, 126.23, 124.50, 121.40, 118.86, 117.83, 105.20, 101.03, 51.67, 38.42, 22.84; EI-MS: m/z 391. Anal. Calcd. For $C_{21}H_{17}N_3O_5$; required: C, 64.45; H, 4.34; N, 10.74%; found: C, 64.42; H, 4.31; N, 10.70%).

4.3.10 1-acetyl-3-(4-hydroxylphenyl)-5-[5-(4-nitrophenyl)-2-furyl]-4,5-dihydro-1H-pyrazole (5j)

Yield 76%; m.p. 114-116°C; IR (KBr): 3550 (O-H str.), 3048 (C=C-H str.), 1669 (C=O str.), 1622 (C=N str.), 1449 (C=C str.), 1140 (C-N str.), 1246 (C-O-C str. sym.), 1045 (C-O-C str. asym.), 1129 (C-OH str.) cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): 1.98 (s, 3H, -$COCH_3$), 3.57 (dd, 1H, Pyrazole-H_A), 3.85 (dd, 1H, Pyrazole-H_B), 5.15 (dd, J = 4.92 & 10.87 Hz, 1H, Pyrazole-H_C), 6.39 (d, J = 3.52 Hz, 1H, Furyl-H_d), 6.89 (d, J = 3.61 Hz, 1H, Furyl-H_e), 6.98 (d, J = 8.34 Hz, 2H, Ar-$H_{a,a'}$); 7.72 (d, J = 8.89 Hz, 2H, Ar-$H_{b,b'}$), 7.76 (d, J = 8.96 Hz, 2H, Ar-$H_{c,c'}$), 8.32 (d, J = 9.01 Hz, 2H, Ar-$H_{d,d'}$), 9.48 (s, 1H, -OH); ^{13}C NMR (101 MHz, DMSO-d_6, δppm) 168.50, 160.85, 152.29, 151.68, 150.02, 147.90, 136.41, 129.08, 126.32, 124.46, 116.04, 105.23, 101.02, 51.60, 38.10, 22.82; EI-MS: m/z 391. Anal. Calcd. For $C_{21}H_{17}N_3O_5$; required: C, 64.45; H, 4.34; N, 10.74%; found: C, 64.44; H, 4.33; N, 10.69%).

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