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Original article

Convenient access to 1,3,4-trisubstituted pyrazoles carrying 5-nitrothiophene moiety via 1,3-dipolar cycloaddition of sydnones with acetylenic ketones and their antimicrobial evaluation

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Abstract

Novel 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl-pyrazoles **7** have been synthesized by the 1,3-dipolar cycloaddition of 3-arylsydnones **3** with 1-aryl-3-(5-nitro-2-thienyl)-2-propyn-1-ones **6**. The newly synthesized compounds were well characterized by elemental analysis, IR, ^{1}H NMR and mass spectral studies. They were also screened for their antibacterial and antifungal activities against a variety of microorganisms and the results of such studies have been discussed in this article.

Keywords: Sydnone; Pyrazole; Acetylenic ketone; 1,3-Dipolar cycloaddition; 5-Nitrothiophene; Antibacterial; Antifungal

1. Introduction

Chemotherapeutic activity of nitro heterocycles is almost always associated with compounds having the nitro group attached to C-5 of the five memebered heterocycles containing appropriate substituents at C-2 [1].

The pyrazole nucleus constitute an interesting class of organic compound with diverse chemical applications [2]. They possess antipyretic, antitumour, tranquilizing and herbicidal activities. Sydnones are easily accessible aromatic compounds and versatile synthetic intermediates with a masked azomethine imine unit. The 1,3-dipolar cycloaddition reaction with various dipolarophiles offers a convenient synthetic route for the preparation of pyrazole derivatives and has been studied extensively pretty long back [3–6]. However, less attention has been paid on the regiochemistry of 1,3-dipolar cycloaddition of sydnones with more complex dipolarophiles. In literature the reaction of sydnones with symmetrical dipolarophiles like dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate has been reported. But less attention was given for the reaction between sydnones and unsymmetrical acetylenic ketones (dipolarophiles).

The incorporation of 5-nitrofuran or 5-nitrothiophene moiety into various heterocyclic systems has found to increase their biological activities. We have reported a few heterocyclic systems carrying 5-nitrofuran moiety as potent antimicrobial agents [7]. In continuation of our studies on 1,3-dipolar cycloaddition reactions of sydnones with dipolarophiles carrying nitrofuran or nitrothiophene moiety [8], we herein report the synthesis of some new pyrazoles possessing 5-nitrothiophene nucleus and evaluated them for their biological properties. The results of such studies are discussed in this article.

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2. Chemistry

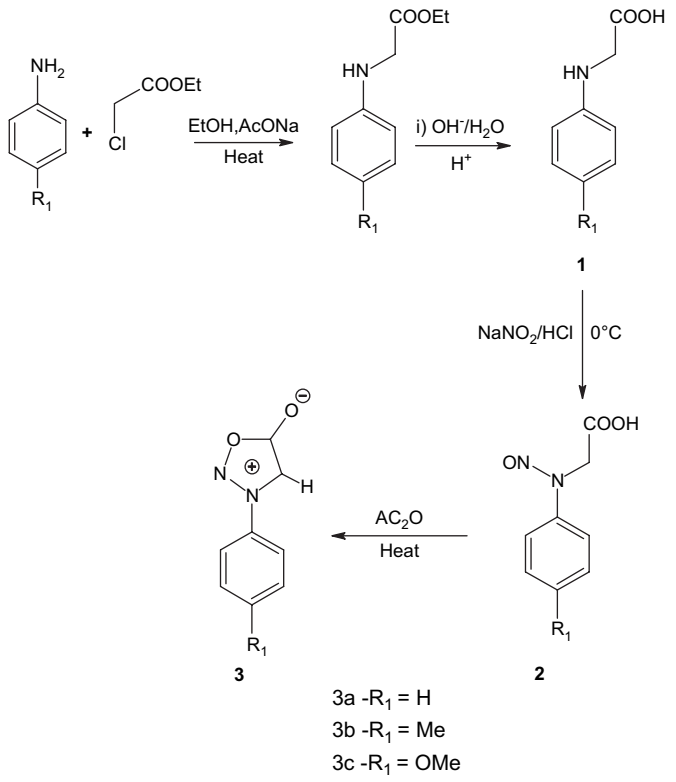
In continuation of our earlier work we studied the 1,3-dipolar cycloaddition [9] reaction of 3-arylsydnone with acetylenic ketones carrying 5-nitrothiophene [10] moiety. Substituted anilines when treated with ethyl chloroacetate in the presence of sodium acetate in ethanol medium gave the corresponding anilino acetic ester. This ester on hydrolsis gave the corresponding aniline acetic acid **1**. Diazotization of the anilino aceticacid **1** with sodium nitrite and conc. HCl at 0 °C gave the corresponding nitroso compound **2**. Cyclisation of this nitroso compound with acetic anhydride gave 3-arylsydnone **3** (Scheme 1). The various acetylenic ketones **6** were obtained by the dehydrobromination of corresponding dibromides **5.** Dibromides **5** were obtained by the bromination of propenones **4**. Propenones **4** were inturn obtained by the condensation of appropriate aryl ketone with 5-nitro thiophenediacetate in ethanol medium employing conc. sulphuric acid as the catalyst (Scheme 2).

The title compounds 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl-pyrazoles **7** were obtained by the treatment of acetylenic ketones **6** with 3-arylsydnones **3** in dry xylene under reflux (Scheme 3). The structures of the newly synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral studies.

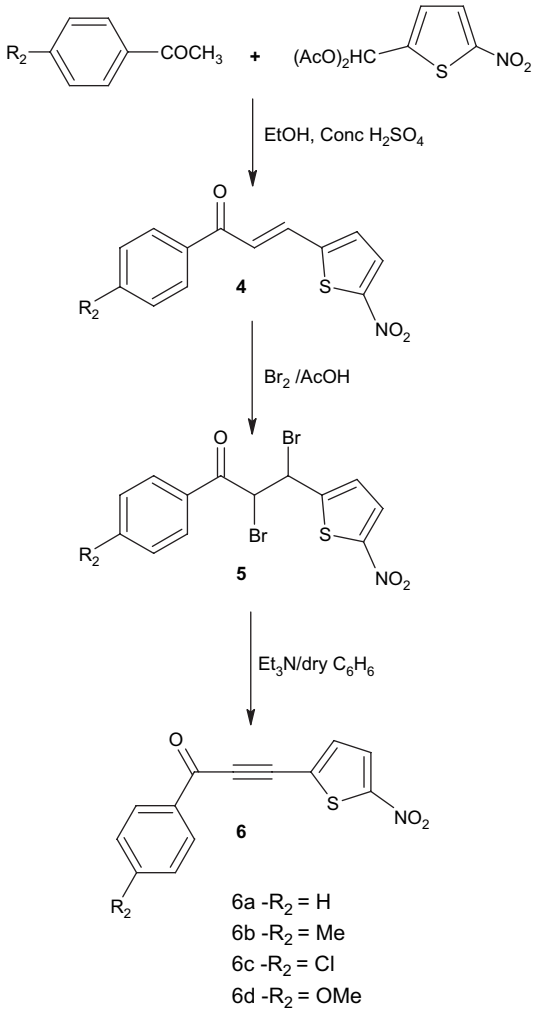
3. Biological activity

The newly synthesized pyrazoles **7** were screened for their antibacterial and antifungal activities. The antibacterial activity was studied against four bacterial strains, namely *Escherichia coli* (ATCC-25922), *Staphylococcus aureus* (ATCC-25923), *Pseudomonas aeruginosa* (ATCC-27853), *Bacillus subtilis* (recultured) and antifungal activity was studied against a fungi namely *Candida albicans* (NCIM No. 3100) by serial dilution method [11,12].

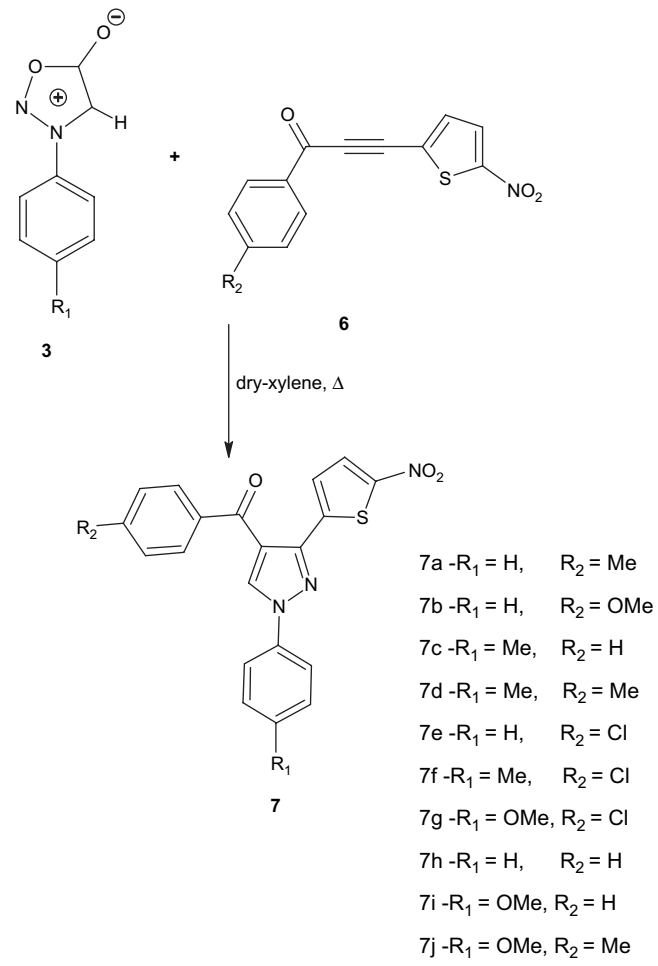
The test compound was dissolved in dimethylformamide (5 mL) to prepare a stock solution of concentration 1000 (μg/mL). One loop full of an 18-h broth culture was inoculated into 5 mL of nutrient broth and this was incubated at 37 °C for 4 h. An assay was prepared by diluting with labeled test tubes 1–11. An aliquot 0.5 mL of stock solution of test compound was added to the first tube. The solution was mixed well and 0.5 mL of this solution was transferred into second tube. This process was repeated serially to obtain the quantities indicated in each of the test tubes. The eleventh tube was taken as growth control. Drops of diluted broth culture of the test organism (approximately 0.5 mL) were added into all the tubes using a sterilized Pasteur pipette. The solutions were mixed gently and the incubation was carried out at 37 °C for 16–18 h. Nitrofurazone dissolved in dimethylformamide was used as standard drug for antibacterial study and fluconazole



Scheme 1.



Scheme 2.



Scheme 3.

was employed as the standard for antifungal studies. The concentration at which there was no turbidity was taken as minimum inhibitory concentration (MIC) and the results are tabulated in Table 1.

4. Results and discussion

The antibacterial and antifungal screenings revealed that some of the tested compounds showed good inhibition at 0.125 μg/mL concentration. The antibacterial screening indicated that among the tested compounds **7d**, **7e** and **7f** showed excellent activity against all the tested bacterial strains namely *S. aureus*, *E. coli*, *P. aeruginosa* and *B. subtilis*. The remaining compounds were found to be moderately active.

The antifungal screening revealed that among the tested compounds **7d**, **7e**, **7f** and **7g** showed excellent activity against the tested fungal strain namely *C. albicans*. The remaining compounds were also equipotent as that of the standard drug. The higher potency of compounds **7d**, **7e** and **7f** may be due to the presence of chlorine in the aryl moiety. So these pyrazoles may be suitable as possible antimicrobial agents. 1,3-Dipolar cycloaddition reaction of sydnones with acetylenic ketones containing 5-nitrothiophene moiety in it has resulted in the formation of biologically active pyarazoles.

5. Conclusions

A series of pyrazoles namely 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl pyrazoles have been synthesized and screened for their antibacterial and antifungal activities. The antibacterial and antifungal screening results suggest that among the compounds tested **7d**, **7e** and **7f** have exhibited higher activity against all the tested microorganisms compared to the standard. Pyrazole nucleus is one of the active components present in many standard drugs. The presence of 5-nitrothiophene moiety is also instrumental in contributing to the net biological activity of the system.

6. Experimental protocols

6.1. General

Melting points were determined using open capillary method and are uncorrected. All compounds were analyzed

Table 1
Antibacterial and antifungal activity data of compounds **7a–j**

Compound	Antibacterial activity (MIC in μg/mL)				Antifungal activity (MIC in μg/mL)
	S. aureus	*E. coli*	*P. aeruginosa*	*B. subtilis*	*C. albicans*
7a	0.25	0.25	0.25	0.25	0.25
7b	0.25	0.25	0.25	0.25	0.25
7c	0.25	0.25	0.25	0.25	0.25
7d	*0.125*	*0.125*	*0.125*	*0.125*	*0.125*
7e	*0.125*	*0.125*	*0.125*	*0.125*	*0.125*
7f	*0.125*	*0.125*	*0.125*	*0.125*	*0.125*
7g	*0.25*	*0.25*	*0.25*	*0.25*	*0.125*
7h	0.25	0.25	0.25	0.25	0.25
7i	0.25	0.25	0.25	0.25	0.25
7j	0.25	0.25	0.25	0.25	0.25
Standard: nitrofurazone	0.25	0.25	0.25	0.25	–
Standard: fluconazole	–	–	–	–	0.25
Control: DMF	–	–	–	–	–

satisfactorily for C, H, and N. The IR spectra (in KBr pellets) were recorded on a JASCO FT IR 430 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) NMR spectrometer using TMS as an internal standard. The chemical shifts are expressed in δ scale downfield from TMS and proton signals are indicated as s = singlet, d = doublet, t = triplet, q = quartet m = multiplet. The mass spectra were recorded either on a Jeol JMS-D 300 mass spectrometer or API 3000 LCMS instrument operating at 70 eV.

6.2. General procedure for the synthesis of N-substituted glycines (anilino acetic acid) **1a–c**

A mixture of substituted aniline (0.5 mol), ethyl chloroacetate (73.0 g 0.6 mol) and anhydrous sodium acetate (50 g, 0.6 mol) in 120 mL of ethanol was refluxed in an oil bath (120–125 °C) for 6 h. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of *N*-substituted glycine without further purification was used for the next step.

To ethyl ester of *N*-substituted glycine (0.4 mol), sodium hydroxide (18 g, 0.45 mol) in 200 mL of water was added and refluxed for 0.5 h. After cooling, the reaction mixture was acidified to pH = 2 using hydrochloric acid. The precipitated *N*-substituted glycine **1** was filtered and washed thoroughly with cold water. Further purification was done by recrystallisation from ethanol. The compounds prepared by this procedure are anilino acetic acid **1a**: m.p. 127–28 °C, yield 70% (lit. [7] 128–29 °C), *p*-methylanilino acetic acid **1b**: m.p. 163–64 °C, yield 75% (lit. [7] 163–64 °C), *p*-methoxyanilino acetic acid **1c**: m.p. 142 °C, yield 75% (lit. [7] 144–45 °C).

6.3. Preparation of N-nitroso-N-substituted glycines **2a–c**

To a stirred suspension of *N*-substituted glycine **1** (0.1 mol) in water at 120 mL at 0 °C, a solution of sodium nitrite (6.9 g, 0.1 mol) in water 24 mL was added drop wise during 30 min. The reaction mixture was practically clear after 2 h. It was filtered and acidified with concentrated hydrochloric acid. The precipitated product was filtered, washed with cold water and dried in air. The nitrosoglycines **2** prepared by the above method were recrystallised from aqueous ethanol. Compounds prepared according to this procedure are *N*-nitroso-*N*-phenylglycine **2a**: m.p. 101–02 °C, yield 80% (lit. [7] 102–03 °C), *N*-nitroso-*N*-(*p*-tolyl)glycine **2b**: m.p. 98–99 °C, yield 83% (lit. [7] 99–100 °C), *N*-nitroso-*N*-(*p*-anisyl)glycine **2c**: m.p. 120–21 °C, yield 84% (lit. [7] 121 °C).

6.4. Preparation of 3-arylsydnone **3a–c**

N-Nitroso-*N*-substituted glycine **2a–c** (0.1 mol) was heated with acetic anhydride (56 mL, 0.5 mol) on a water bath for 2–4 h. The reaction mixture was kept aside at room temperature for overnight. Then it was poured into ice-cold water, filtered and washed with water, 5% sodium bicarbonate solution and again with water. The solid was dried and recrystallised from benzene. Compounds prepared according to this procedure are 3-phenylsydnone **3a**: m.p. 134–35 °C, yield 73% (lit. [7] 134–35 °C), 3-(*p*-tolyl)sydnone **3b**: m.p. 143–44 °C, yield 78%. (lit. [7] 144–45 °C), 3-(*p*-anisyl)sydnone **3c**: m.p. 125–26 °C, yield 75%. (lit. [7] 125–26 °C).

6.5. General procedure for the preparation of 1-aryl-3-(5-nitro-2-thienyl)-2-propen-1-ones **4a–d**

A solution of 5-nitro-2-thiophenealdehyde diacetate (2.5 g, 0.01 mol) and an appropriate acetophenone (0.01 mol) in ethanol (20 mL) was treated with conc. sulfuric acid (2 mL). The mixture was stirred for 4 h and allowed to stand at room temperature for 24 h. The precipitated crystals of propenones were collected by filtration, washed with ethanol, dried and recrystallised from ethanol. Characterization data of the compounds prepared as per this procedure is given in Table 2.

6.6. General procedure for the preparation of 2,3-dibromo-1-aryl-3-(5-nitro-2-thienyl)propan-1-ones **5a–d**

1-Aryl-3-(5-nitro-2-thienyl)-2-propen-1-one **4** (0.01 mol) was dissolved in glacial acetic acid (25 mL) by gentle warming. A solution of bromine in glacial acetic acid (30% w/v) was added to it with constant stirring till the yellow color of bromine persisted. The reaction mixture was kept aside at room temperature overnight. Crystals of dibromopropanones separated out. They were collected by filtration and washed with ethanol. It was dried and recrystallised from glacial acetic acid. Characterization data of the compounds prepared as per this procedure is given in Table 3.

6.7. General procedure for the preparation of 1-aryl-3-(5-nitro-2-thienyl)-2-propyn-1-ones **6a–d**

To a stirred solution of 2,3-dibromo-1-aryl-3-(5-nitro-2-thienyl)propan-1-one (0.01 mol) **5** in dry benzene (100 mL), a solution of triethylamine (4 g, 0.04 mol) in dry benzene (30 mL) was added. The reaction mixture was stirred at room temperature for 24 h. The resulting mass of

Table 2
Characterization data of 1-aryl-3-(5-nitro-2-thienyl)-2-propen-1-ones: **4a–d**

Compound	R_2	M.p. (°C)	Crystal nature
4a	H	176–77 (177)	Yellowish flakes
4b	Me	169–70 (170)	Brown crystals
4c	Cl	224–25 (225)	Yellow needles
4d	OMe	207 (207)	Yellow needles

The values within the parenthesis indicate the literature [8] melting point.

Table 3
Characterization data of 2,3-dibromo-1-aryl-3-(5-nitro-2-thienyl) propan-1-ones: **5a–d**

Compound	R_2	M.p. (°C)	Crystal nature
5a	H	144–45 (145)	Brown crystals
5b	Me	150–52 (151)	Brown needles
5c	Cl	170–71 (170)	Pale yellow crystals
5d	OMe	158–59 (159)	Shining yellow crystals

The values within the parenthesis indicate the literature [8] melting point.

Table 4
Characterization data of 1-aryl-3-(5-nitro-2-thienyl)-2-propyn-1-ones: **6a–d**

Compound	R_2	M.p. (°C)	Crystal nature
6a	H	154–56 (155)	Brown crystals
6b	Me	152–53 (153)	Brown crystals
6c	Cl	181–82 (182)	Brown crystals
6d	OMe	165–67 (167)	Yellowish needles

The values within the parenthesis indicate the literature [8] melting point.

triethylamine hydrobromide was removed by filtration and the filtrate was concentrated by distilling the benzene under reduced pressure. The concentrated solution was cooled to room temperature. The product that formed was collected by filtration and washed with ethanol. It was dried and recrystallised from ethanol. Characterization data of the compounds prepared as per this procedure are given in Table 4.

*6.8. General procedure for the synthesis of 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl pyrazoles **7a–j***

3-Arylsydnone **3** (0.01 mol) and 1-aryl-3-(5-nitro-2-thienyl)-2-propyn-1-one **6** (0.01 mol) were dissolved in 10 mL dry xylene and refluxed for 3–4 h. After completion of the reaction (monitored by TLC and evolution of CO_2) the solvent was removed by distillation under reduced pressure. The crude product obtained was purified by recrystallisation from ethanol and DMF mixture. The yield, melting point and other characterization data of these compounds are given in Table 5.

*6.8.1. Data for compounds **7a–j***

*6.8.1.1. Compound **7a**: 1-phenyl-3-(5-nitro-2-thienyl)-4-(p-methylbenzoyl) pyrazole*. ^{1}H NMR ($CDCl_3$) δ: 2.423 (s, 3H, CH_3), 7.32 (d, 1H, thiophene-3-H), 7.89 (d, 1H, thiophene 4-H), 7.45 (d, 2H, *o*-protons of *p*-tolyl, $J = 10.5$ Hz), 7.98 (d, 2H, *m*-protons of *p*-tolyl, $J = 10.5$ Hz), 7.52–7.63 (m, 5H, Ar–H), 8.19 (s, 1H, pyrazole-5H); LCMS, *m/z*; 390 ($M^+ + 1$).

*6.8.1.2. Compound **7b**: 1-phenyl-3-(5-nitro-2-thienyl)-4-p-(methoxybenzoyl) pyrazole*. ^{1}H NMR ($CDCl_3$) δ: 3.77 (s, 3H, OCH_3), 7.02 (d, 1H, thiophene-3-H), 7.66 (d, 1H, thiophene 4-H), 7.52 (d, 2H, *o*-protons of *p*-anisyl, $J = 11.6$ Hz), 7.88 (d, 2H, *m*-protons of *p*-anisyl, $J = 11.6$ Hz), 7.53–7.63 (m, 5H, Ar–H), 8.13 (s, 1H, pyrazole-5H); LCMS, *m/z*; 405 ($M^+ + 1$).

*6.8.1.3. Compound **7c**: 1-p-tolyl-3-(5-nitro-2-thienyl)-4-benzoyl pyrazole*. ^{1}H NMR ($CDCl_3$) δ: 2.46 (s, 3H, CH_3), 7.33 (d, 1H, thiophene-3-H), 7.92 (d, 1H, thiophene 4-H), 7.44 (d, 2H, *o*-protons of *p*-tolyl, $J = 10.1$ Hz), 8.05 (d, 2H, *m*-protons of *p*-tolyl, $J = 10.1$ Hz), 7.52–7.88 (m, 5H, Ar–H), 8.23 (s, 1H, pyrazole-5H); LCMS, *m/z*; 390 ($M^+ + 1$).

*6.8.1.4. Compound **7d**: 1-p-tolyl-3-(5-nitro-2-thienyl)-4-(p-methylbenzoyl) pyrazole*. IR (KBr,γ cm^{-1}); 1646 (C=O), 1577 (C=N), 1524 (NO_2– asymmetric), 1339 (NO_2– symmetric); ^{1}H NMR ($CDCl_3$) δ: 2.42 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.41 (d, 1H, thiophene-3-H), 8.05 (d, 1H, thiophene 4-H), 7.26 (d, 2H, *o*-protons of *p*-tolyl, $J = 9.8$ Hz), 7.80 (d, 2H, *m*-protons of *p*-tolyl, $J = 9.8$ Hz), 7.61 (d, 2H-*o*-protons of *p*-tolyl, $J = 10.2$ Hz), 7.87 (d, 2H, *m*-protons of *p*-tolyl, $J = 10.2$ Hz), 8.19 (s, 1H, pyrazole-5H);LCMS, *m/z*; 403 ($M^+ + 1$).

*6.8.1.5. Compound **7f**: 1-p-tolyl-3-(5-nitro-2-thienyl)-4-(p-chlorobenzoyl) pyrazole*. IR (KBr,γ cm^{-1}); 1634 (C=O), 1523 (C=N), 1413 (NO_2– asymmetric), 1333 (NO_2– symmetric); ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 7.35 (d, 1H, thiophene-3-H), 7.97 (d, 1H, thiophene 4-H), 7.54 (d, 2H, *o*-protons of *p*-tolyl, $J = 10.5$ Hz), 7.85 (d, 2H, *m*-protons of *p*-tolyl, $J = 10.5$ Hz), 7.66 (d, 2H-*o*-protons of *p*-chlorophenyl, $J = 11.7$ Hz), 7.89 (d, 2H-*m*-protons of *p*-chlorophenyl, $J = 11.7$ Hz), 8.18 (s, 1H, pyrazole-5H); LCMS, *m/z*; 424 ($M^+ + 1$).

*6.8.1.6. Compound **7g**: 1-p-anisyl-3-(5-nitro-2-thienyl)-4-(p-cholorbenzoyl) pyrazole*. ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, 3H, OCH_3), 7.05 (d, 1H, thiophene-3-H), 7.97 (d, 1H, thiophene-4-H), 7.51 (d, 2H, *o*-protons of *p*-anisyl, $J = 11.6$ Hz), 7.67 (d, 2H, *m*-protons of *p*-anisyl, $J = 11.6$ Hz), 7.53 (d, 2H-*o*-protons of *p*-chlorophenyl, $J = 11.9$ Hz), 7.83 (d, 2H-*m*-protons of *p*-chlorophenyl, $J = 11.9$ Hz), 8.13 (s, 1H, pyrazole-5H); LCMS, *m/z*; 440 ($M^+ + 1$).

*6.8.1.7. Compound **7h**: 1-phenyl-3-(5-nitro-2-thienyl)-4-benzoyl pyrazole*. ^{1}H NMR ($CDCl_3$) δ: 7.06 (d, 1H, thiophene-3-H), 7.56 (d, 1H, thiophene-4-H), 7.58–7.64 (m, 10H, Ar–H), 8.11 (s, 1H, pyrazole-5H); LCMS, *m/z*; 376($M^+ + 1$).

*6.8.1.8. Compound **7j**: 1-phenyl-3-(5-nitro-2-thienyl)-4-(p-methylbenzoyl) pyrazole*. ^{1}H NMR ($CDCl_3$) δ: 1.56 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.66 (d, 1H, thiophene-3-H), 7.99 (d, 1H, thiophene-4-H), 7.02 (d, 2H, *o*-protons of *p*-tolyl, $J = 11.5$ Hz), 7.56 (d, 2H, *m*-protons of *p*-tolyl, $J = 11.5$ Hz), 7.68 (d, 2H-*o*-protons of *p*-anisyl, $J = 11.6$ Hz), 7.89 (d, 2H-*m*-protons of *p*-anisyl,

Table 5
Characterization data of 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl pyrazoles **7a–j**

Compound	R_1	R_2	Molecular formula	M.p. (°C)	Yield (%)	Crystal nature	Percentage analysis found (calculated)		
							C	H	N
7a	H	Me	$C_{21}H_{15}N_3O_3S$	145–47	71	Bright yellow	64.79 (64.78)	3.86 (3.85)	10.76 (10.79)
7b	H	OMe	$C_{21}H_{15}N_3O_4S$	200–02	73	Bright yellow	62.10 (62.2)	3.69 (3.7)	10.29 (10.3)
7c	Me	H	$C_{21}H_{15}N_3O_3S$	182–84	75	Light yellow	64.65 (64.78)	3.86 (3.85)	10.78 (10.79)
7d	Me	Me	$C_{22}H_{17}N_3O_3S$	135–37	73	Light yellow	65.49 (65.5)	4.20 (4.21)	10.41 (10.42)
7e	H	Cl	$C_{20}H_{12}N_3O_3SCl$	205–07	72	Bright yellow	58.59 (58.61)	2.91 (2.93)	10.23 (10.25)
7f	Me	Cl	$C_{21}H_{14}N_3O_3SCl$	195–97	77	Bright yellow	59.49 (59.51)	3.29 (3.30)	9.89 (9.91)
7g	OMe	Cl	$C_{21}H_{14}N_3O_4SCl$	150–52	78	Bright yellow	57.37 (57.34)	3.23 (3.18)	9.38 (9.55)
7h	H	H	$C_{20}H_{13}N_3O_3S$	125–27	80	Light yellow	63.9 (64)	4.85 (4.87)	11.19 (11.2)
7i	OMe	H	$C_{22}H_{15}N_3O_4S$	127–29	75	Bright yellow	62.19 (62.2)	3.69 (3.7)	10.31 (10.3)
7j	OMe	Me	$C_{22}H_{17}N_3O_4S$	108–09	76	Bright yellow	63.1 (63)	4.09 (4.05)	10.01 (10.02)

Solvent for recrystallisation: ethanol:DMF:: 4:2.

$J = 11.6$ Hz), 8.15 (s, 1H, pyrazole-5H); LCMS, *m/z*; 420 ($M^+ + 1$).

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