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Short Report

# Regiospecific Synthesis of New Non-Condensed Heteropolycyclic Systems from β-Heteroaryl-β-methoxyvinyl Trihalomethyl Ketones

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Reações de ciclo-condensação envolvendo 1,1,1-trifluor(cloro)-4-metoxi-4-(2-heteroaril)-3-buten-2-onas (β-alcoxivinil trialometil cetonas) e furoil-, tenoil- e isonicotinoil-hidrazinas (heteroarilhidrazidas), realizadas sob condições brandas e em meio alcoólico, forneceram em passo reacional único e regioespecificamente, uma série inédita composta por doze heteroaroil-2-pirazolinas trialometil heteroaril substituídas em rendimentos de 50-78%; um novo sistema heteropolicíclico não condensado.

A novel series of twelve heteroaroyl-2-pyrazolines trihalomethyl and substituted heteroaryl, as non-condensed heteropolycyclic systems, have been synthesized in one-step in 50-78% yield from the regiospecific cyclocondensation reaction of 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl)- and 4-(2-thienyl)-3-buten-2-ones (β-alkoxyvinyl trihalometil ketones) with furoic hydrazide, 2-thiophenecarboxylic hydrazide and isonicotinic acid hydrazide (heteroaroylhydrazines) under mild conditions in methanol as solvent.

**Keywords:** 2-pyrazolines, pyrazoles, 4-alkoxy-1,1,1-trihalo-alk-3-en-2-ones, hydrazides, heteroaroylhydrazines, hydrazines

## Introduction

Although many methods have been published for the synthesis of 1*H*-pyrazoles and their derivatives, attempts to perform the synthesis of a simple 4,5-dihydro-1*H*-pyrazoles (2-pyrazolines), has not yet been sucessfully achieved.[1-3] By conventional procedure, pyrazoles have been obtained by directly reacting β-diketones with hydrazine.[1] However, in most cases, 5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been obtained when the N-1 atom is substituted with a strong electron-withdrawing group which stabilizes the –OH group and possibly hinders the elimination of the water molecule and the subsequent aromatization of the pyrazoline ring.[1]

Regarding pharmacological applications, 2-pyrazolines (4,5-dihydro-1*H*-pyrazoles) have been found to possess antitumor,[4] antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal and others properties.[5-16] Some of these compounds also presented anti-inflammatory, anti-diabetic, anesthetic and analgesic properties.[13-15] For example, in a recent work Mamolo *et al.*[16] have synthesized a series of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazoles in a three-step in low yields, which involved an aldol condensation, cyclocondensation with hydrazine and N-acylation with isonicotinoyl chloride. These 2-pyrazolines showed an interesting antimycobacterial activity in vitro.

In 2002, our research group reported[17] a new approach for the synthesis of a series of four ketones as 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl)- and 4-(2-thienyl)-3-buten-2-ones and their 4,4,4-trihalo-1-(2-heteroaryl)-1,3-butanediones derivatives. The autors also showed that mixtures of β-alkoxyvinyl trifluoromethyl ketones and the respective 1,3-butanediones derived from 2-acetylthiophene and 2-acetylfuran react with hydroxylamine hydrochloride, dry hydrazine and thiosemicarbazide hydrochloride leading to 3-(2-thienyl)- and 3-(2-furyl)azoles

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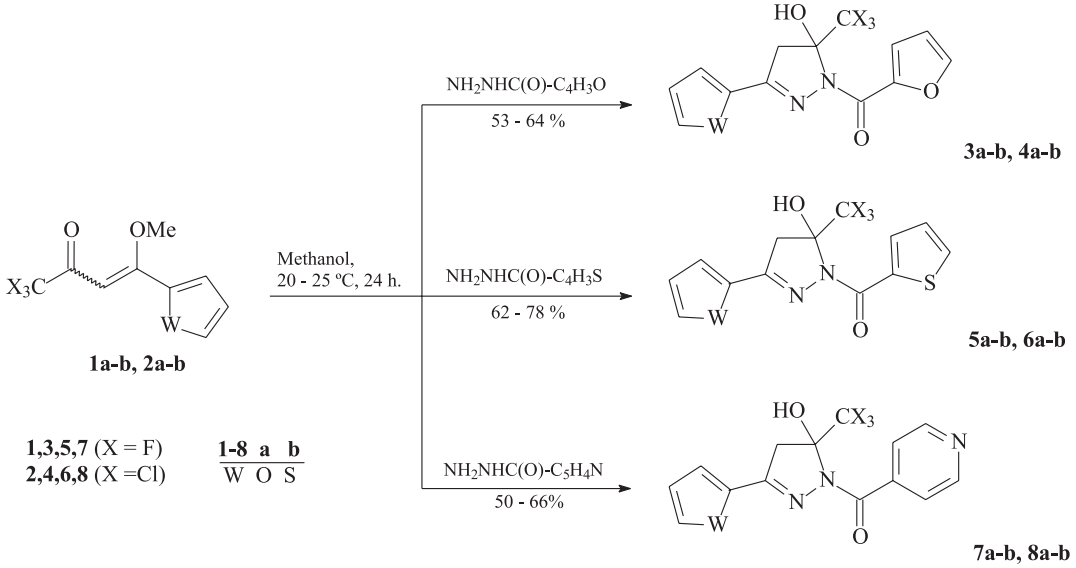
derivatives. In this case, only one isoxazoline and one 2-pyrazoline have been isolated. In particular, the synthetic potential of $\beta$-alkoxyvinyl trihalomethyl ketones to obtain series of novel heterocycles of five,[18] six,[19] seven membered rings[20] and more recently bisheterocyles[21] has been reported by us.

Considering the biological importance of 2-pyrazolines and the fact that trichloromethylated analogs, such as, bisheteroaryl ketones are not yet known, it would be nice to demonstrate a new synthetic application of $\beta$-heteroaryl-$\beta$-methoxyvinyl trihalomethyl ketones.[17] Herein, the synthesis and isolation of a novel series of twelve heteroaroyl pyrazolines trihalomethyl and heteroaryl substituted, a heteropolycyclic system, from the reaction of 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl)- and 4-(2-thienyl)-3-buten-2-ones with furoic hydrazide, 2-thiophenecarboxylic hydrazide and isonicotinic acid hydrazide, is presented (Scheme 1).

## Results and Discussion

The reaction of 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl) and 4-(2-thienyl)-3-buten-2-ones (**1a-b, 2a-b**) with furoic hydrazide, 2-thiophenecarboxylic hydrazide and isonicotinic acid hydrazide was carried out in a 1:1 molar ratio in anhydrous methanol and all reactions were monitored by TLC. The most satisfactory results were obtained when the reactions were performed under mild conditions at room temperature for 24 hours. It was observed that the reactions performed at higher temperatures resulted in polymerization and lower yields. After the addition of the reagents, the contents darkened and formation of brown and gray solids occurred. After 24 hours, the contents were cooled to 10 ºC and the solid products were isolated by filtration. The crude crystals were recrystallized either from methanol or acetone. Under these conditions, the derivatives of these three series of hydrazides, viz., 3-(2-furyl)- or 3-(2-thienyl)-5-hydroxy-5-trifluoro(chloro)methyl-4,5-dihydro-1*H*-1-(2-furoyl)pyrazoles (**3a-b, 4a-b**), 3-(2-furyl)- or 3-(2-thienyl)-5-hydroxy-5-trifluoro(chloro)methyl-4,5-dihydro-1*H*-1-(2-thenoyl)pyrazoles (**5a-b, 6a-b**) and 3-(2-furyl)- or 3-(2-thienyl)-5-hydroxy-5-trifluoro(chloro)methyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazoles (**7a-b, 8a-b**) were obtained regiospecifically in one-step and in satisfactory yields (64 - 53%, 78 - 62% and 66 - 50%), respectively. Our experiments demonstrated that the trihalomethyl and the heteroaroyl groups at the positions 5 and 1 of the 2-pyrazolines **3-8**, respectively, act as protective groups with electron withdrawing effect, thus stabilizing the –OH group at C-5 and possibly hindering the elimination of water and the subsequent aromatization of the five-membered ring. Due to the thermodynamic stability of 2-pyrazolines **3-8**, the presence of a trihalomethyl group on the $\beta$-methoxyvinyl trihalomethyl ketones **1** and **2** and the heteroaroyl groups on the dinucleophiles (hydrazides) were the determining factor of the regiochemistry of the reaction. In addition, the heteroaryl substituent (2-thienyl and 2-furyl) attached at position 4 of the ketones **1** and **2** and the adopted synthetic method produced no observable effects on the regiochemistry of the cyclo-condensation reaction.

The best reaction conditions, selected physical and spectral data are presented in the experimental part. The 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl)- and




**Scheme 1.**

4-(2-thienyl)-3-buten-2-ones **1a-b** and **2a-b** were prepared according to the procedure developed previously.[17]

The unambiguous $^{1}H$ and $^{13}C$ NMR chemical shift assignments of 3-aryl-5-hydroxy-5-trifluoro(chloro)methyl-4,5-dihydro-1*H*-1-(heteroaroyl)pyrazoles (**3a-b, 4a-b, 5a-b, 6a-b 7a-b** and **8a-b**), were made with the help of homo- and heteronuclear COSY, HMQC and HMBC 2D NMR periments and by comparison with NMR data of others 2- pyrazolines previously synthesised in our laboratory. Compounds **3-8** show the $^{1}H$ NMR chemical shifts of the diastereotopic methylene protons ( H4a and H4b) as a characteristic AB system and as a doublet in the range of $\delta$ 3.90 to 4.12 and another doublet in the range of $\delta$ 3.53 to 3.85, respectively, with a *geminal* coupling constant in the range of $^{2}J$ = 18.8 – 19.4 Hz. The trifluoromethylated heterocycles **3a-b, 5a-b** and **7a-b** present the typical $^{13}C$ chemical shifts of pyrazoline ring carbons at $\delta$ 147.4 (C3), 44.1 (C4), 92.1 (C5), 123.4 ($CF_3$). The trichloromethylated compounds **4a-b, 6a-b** and **8a-b** present the typical $^{13}C$ chemical shifts of pyrazoline ring carbons at $\delta$ 148.4 (C3), 46.7 (C4), 102.7 (C5), 103.1 ($CCl_3$). The carbonyl carbon for the trifluoro(chloro)methylated series **3-6** (furoyl and thenoyl derivatives) shows signals in the range of $\delta$ 151.1 to 160.6. As expected, for isonicotinoyl derivatives (**7a-b, 8a-b**) the carbonyl carbon shows signals in the range of $\delta$ 164.8 to 165.4.

## Conclusions

We have developed an useful, simple and convenient procedure to obtain new trifluoro(chloro)methylated hydroxypyrazolines, as heteropolycycles derived from thiophene, furan and pyridine under mild conditions. Furthermore, we have been able to use for the first time b-heteroaryl-b-methoxyvinyl trihalomethyl ketones **1** and **2** in cyclocondensation reactions with heteroaroylhydrazines.

## Experimental

Unless otherwise indicated all common reagents and solvents used in the present work were obtained from commercial suppliers without further purification. All melting points were determined using open capillaries on a Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were acquired on a Bruker DPX 200 spectrometer ($^{1}H$ at 200.13 MHz and $^{13}C$ at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in methyl sulfoxide-$d_6$ for **3a-i** using TMS as internal reference. IR spectra were recorded on a Nicolet Magna 550 IR spectrometer. The CHN elemental analysis were performed on a Perkin–Elmer 2400 CHN elemental analyzer (São Paulo University, USP/ Brazil).

*General procedure for the synthesis of 3-heteroaryl-5-hydroxy-5-trifluoro(trichloro)methyl-4,5-dihydro-1H-1-(heteroaroyl)pyrazoles (**3-8**)*

To a stirred solution of 4-alkoxy-4-heteroaryl-1,1,1-trifluoro(trichloro)-3-buten-2-one **1a-b** or **2a-b** (5 mmoles) in 6 mL of methanol, dry 2-thiophenecarboxylic hydrazide, furoic hydrazide or isonicotinic acid hydrazide (5 mmoles) was added at 20 – 25°C. The mixture was stirred at room temperature (20 – 25°C) for 24 hours. After cooling ( < 10°C), the crystalline solids were isolated by filtration, washed with cold methanol and recrystallized from acetone.

*Data for 3-(2-furyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-(2-furoyl)pyrazole (**3a**)*

Gray crystals (62% yield), mp 166 – 168 °C (acetone). $^{1}H$ NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.35 (1H, s, OH); 3.90 (1H, d, *J* 18.7, H4a); 3.54 (1H, d, *J* 18.8, H4b). (Furoyl) $\delta$ 8.04 (1H, s, H5); 7.64 (1H, d, *J* 3.0, H3); 6.78 – 6.73 (1H, m, H4). (Furyl) $\delta$ 7.99 (1H, s, H5); 7.20 (1H, d, *J* 3.2, H3); 6.78 – 6.73 (1H, m, H4). $^{13}C$ NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 146.0 (C3); 124.6 ($CF_3$, $J_{CF}$ 283.8); 92.0 (C5, $^{2}J$ 34.1); 43.5 (C4). (Furoyl) $\delta$ 155.3 (C=O); 146.8 (C2); 145.5 (C5); 120.3 (C4); 112.0 (C3). (Furyl) $\delta$ 145.2 (C2); 144.0 (C5); 114.9 (C4); 112.3 (C3). IR (KBr) $\nu_{max}$ / $cm^{-1}$: 3329 (OH); 1644 (C=O); 1555, 1468 (C=C). Anal. Calc. for $C_{13}H_9F_3N_2O_4$ (314.22): C, 49.69; H, 2.89; N, 8.92%. Found: C, 50.16; H, 2.84; N, 8.95%.

*Data for 3-(2-thienyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-(2-furoyl)pyrazole (**3b**)*

Gray crystals (53% yield), mp 149 – 150 °C (acetone). $^{1}H$ NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.33 (1H, s, OH); 3.97 (1H, d, *J* 19.2, H4a); 3.62 (1H, d, *J* 19.0, H4b). (Furoyl) $\delta$ 8.01 (1H, s, H5); 7.62 (1H, d, *J* 2.8, H3); 6.75 (1H, dd, *J* 3.4, *J* 1.6, H4). (Thienyl) $\delta$ 7.80 (1H, d, *J* 5.0, H5); 7.53 (1H, d, *J* 3.6, H3); 7.20 (1H, dd, *J* 4.4, *J* 4.2, H4). $^{13}C$ NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 148.8 (C3); 123.2 ($CF_3$, $J_{CF}$ 284.1); 92.5 (C5, $^{2}J$ 33.7); 44.3 (C4). (Furoyl) $\delta$ 151.1 (C=O); 146.9 (C2); 145.5 (C5); 120.1 (C4); 112.1 (C3). (Thienyl) $\delta$ 133.1 (C2); 131.3 (C3); 130.2 (C5); 128.3 (C4). IR (KBr) $\nu_{max}$ / $cm^{-1}$: 3242 (OH); 1645 (C=O); 1560, 1470 (C=C). Anal. Calc. for $C_{13}H_9F_3N_2O_3S$ (330.28): C, 47.28; H, 2.75; N, 8.48%. Found: C, 47.53; H, 2.70; N, 8.58%.

*Data for 3-(2-furyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1H-1-(2-furoyl)pyrazole (**4a**)*

Gray crystals (61% yield), mp 162 – 164 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.25 (1H, s, OH); 3.97 (1H, d, *J* 19.4, H4a); 3.70 (1H, d, *J* 19.2, H4b). (Furoyl) $\delta$ 8.02 (1H, s, H5); 7.57 (1H, d, *J* 3.4, H3); 6.76 – 6.71 (1H, m, H4). (Furyl) $\delta$ 7.97 (1H, d, *J* 1.2, H5); 7.24 (1H, d, *J* 3.2, H3); 6.76 – 6.71 (1H, m, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 146.2 (C3); 103.1 ($CCl_3$); 102.5 (C5); 46.1 (C4). (Furoyl) $\delta$ 157.2 (C=O); 146.9 (C2); 145.5 (C5); 120.7 (C4); 112.1 (C3). (Furyl) $\delta$ 145.6 (C2); 144.8 (C5); 115.3 (C4); 112.3 (C3). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3288 (OH); 1639 (C=O); 1554, 1470 (C=C). Anal. Calc. for $C_{13}H_9Cl_3N_2O_4$ (363.58): C, 42.95; H, 2.50; N, 7.70%. Found: C, 43.17; H, 2.40; N, 7.65%.

*Data for 3-(2-thienyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1H-1-(2-furoyl)pyrazole (**4b**)*

Gray crystals (64% yield), mp 139 – 141 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.25 (1H, s, OH); 4.09 (1H, d, *J* 19.0, H4a); 3.80 (1H, d, *J* 19.2, H4b). (Furoyl) $\delta$ 8.02 (1H, s, H5); 7.68 (1H, d, *J* 2.4, H3); 6.76 (1H, dd, *J* 3.4, *J* 1.8, H4). (Thienyl) $\delta$ 7.81 (1H, d, *J* 4.2, H5); 7.50 (1H, d, *J* 3.2, H3); 7.21 (1H, dd, *J* 4.8, *J* 3.6, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 150.4 (C3); 103.2 ($CCl_3$); 103.1 (C5); 46.9 (C4). (Furoyl) $\delta$ 157.0 (C:O); 146.9 (C2); 145.5 (C5); 120.4 (C4); 112.1 (C3). (Thienyl) $\delta$ 132.8 (C2); 131.4 (C3); 130.4 (C5); 128.3 (C4). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3145 (OH); 1629 (C=O); 1550, 1461 (C=C). Anal. Calc. for $C_{13}H_9Cl_3N_2O_3S$ (379.65): C, 41.13; H, 2.39; N, 7.38%. Found: C,41.41; H, 2.44; N, 7.38%.

*Data for 3-(2-furyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-(2-thenoyl)pyrazole (**5a**)*

Gray crystals (67% yield), mp 150 – 152 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.28 (1H, s, OH); 3.90 (1H, d, *J* 18.8, H4a); 3.53 (1H, d, *J* 18.8, H4b). (Thenoyl) $\delta$ 8.11 (1H, dd, *J* 3.8, *J* 1.4, H3); 7.98 – 7.97 (1H, m, H5); 7.23 (1H, dd, *J* 4.8, *J* 4.0, H4). (Furyl) $\delta$ 7.98 – 7.97 (1H, m, H5); 7.17 (1H, d, *J* 3.6, H3); 6.73 (1H, dd, *J* 3.6, *J* 1.6, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 146.2 (C3); 123.1 ($CF_3$, $J_{CF}$ 283.5); 91.9 (C5, $^2J$ 34.5); 43.7 (C4). (Thenoyl) $\delta$ 158.7 (C=O); 135.3 (C5); 135.2 (C3); 134.8 (C2); 127.1 (C4). (Furyl) $\delta$ 145.1 (C2); 143.6 (C5); 115.1 (C4); 112.4 (C3). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3309 (OH); 1620 (C=O), 1512, 1440 (C=C). Anal. Calc. for $C_{13}H_9F_3N_2O_3S$ (330.28): C, 47.28; H, 2.75; N, 8.48%. Found: C, 47.75; H, 2.76; N, 8.76%.

*Data for 3-(2-thienyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-(2-thenoyl)pyrazole (**5b**)*

Gray crystals (78% yield), mp 155 – 157 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.29 (1H, s, OH); 4.00 (1H, d, *J* 18.8, H4a); 3.64 (1H, d, *J* 19.2, H4b). (Thenoyl) $\delta$ 8.08 (1H, dd, *J* 4.2, *J* 1.4, H3); 7.99 (1H, dd, *J* 4.8, *J* 1.2, H5); 7.25 – 7.21 (1H, m, H4). (Thienyl) $\delta$ 7.81 (1H, d, *J* 5.2, H5); 7.62 (1H, d, *J* 4.0, H3); 7.25 – 7.21 (m, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 148.2 (C3); 123.1 ($CF_3$, $J_{CF}$ 284.6); 92.4 (C5, $^2J$ 33.8); 44.5 (C4). (Thenoyl) $\delta$ 158.4 (C=O); 135.4 (C5); 135.3 (C3); 134.6 (C2); 127.0 (C4). (Thienyl) $\delta$ 133.0 (C2); 131.3 (C3); 130.5 (C5); 128.3 (C4). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3298 (OH); 1619 (C=O); 1510, 1450 (C=C). Anal. Calc. for $C_{13}H_9F_3N_2O_2S_2$ (346.34): C, 45.08; H, 2.62; N, 8.09%. Found: C, 45.56; H, 2,60; N, 8.26%.

*Data for 3-(2-furyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1H-1-(2-thenoyl)pyrazole (**6a**)*

Gray crystals (66% yield), mp 125 – 127 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.24 (1H, s, OH); 4.00 (1H, d, *J* 19.2, H4a); 3.76 (1H, d, *J* 19.2, H4b). (Thenoyl) $\delta$ 8.09 (1H, dd, *J* 3.8, *J* 1.4, H3); 7.99 – 7.97 (1H, m, H5); 7.22 (1H, m, H4). (Furyl) $\delta$ 7.99 – 7.97 (1H, m, H5); 7.22 (1H, m, H3); 6.73 (1H, dd, *J* 3.6, *J* 2.0, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 146.3 (C3); 103.1 ($CCl_3$); 102.4 (C5); 46.2 (C4). (Thenoyl) $\delta$ 160.6 (C=O); 135.4 (C5); 135.3 (C3); 134.8 (C2); 127.0 (C4). (Furyl) $\delta$ 145.2 (C2); 144.7 (C5); 115.5 (C4); 112.4 (C3). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3329 (OH); 1634 (C=O); 1512, 1487 (C=C). Anal. Calc. for $C_{13}H_9Cl_3N_2O_3S$ (379.65): C, 41.13; H, 2.39; N, 7.38%. Found: C, 41.46; H, 2.39; N, 7.19%.

*Data for 3-(2-thienyl)-5-hydroxy-5-trichloromethyl4,5-dihydro-1H-1-(2-thenoyl)pyrazole (**6b**)*

Gray crystals (62% yield), mp 160 – 162 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.25 (1H, s, OH); 4.12 (1H, d, *J* 19.2, H4a); 3.85 (1H, d, *J* 19.2, H4b). (Thenoyl) $\delta$ 8.07 (1H, dd, *J* 3.8, *J* 1.0, H3); 8.00 (1H, dd, *J* 5.0, *J* 1.0, H5); 7.24 – 7.21 (1H, m, H4). (Thienyl) $\delta$ 7.83 (1H, d, *J* 4.8, H5); 7.69 (1H, d, *J* 3.2, H3); 7.24 - 7.21 (1H, m, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 149.9 (C3); 103.0 ($CCl_3$); 102.9 (C5); 47.1 (C4). (Thenoyl) $\delta$ 160.2 (C=O); 135.6 (C5); 135.4 (C3); 134.5 (C2); 126.9 (C4). (Thienyl) $\delta$ 132.7 (C2); 131.5 (C3); 130.7 (C5); 128.2 (C4). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3165 (OH); 1605 (C=O); 1509, 1419 (C=C). Anal. Calc. for $C_{13}H_9Cl_3N_2O_2S_2$ (395.71): C, 39.46; H, 2.29; N, 7.08%. Found: C, 39.30; H, 2.00; N, 6.69%.

*Data for 3-(2-furyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-(isonicotinoyl)pyrazole (**7a**)*

Gray crystals (66% yield), mp 164 – 166 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.48 (1H, s, OH); 3.91 (1H, d, *J* 19.2, H4a); 3.54 (1H, d, *J* 19.0, H4b). (Isonicotinoyl) $\delta$ 8.74 (1H, s, 2H, Py); 7.59 (2H, d, *J* 5.6, Py). (Furyl) $\delta$ 7.87 (1H, s, H5); 7.10 (1H, d, *J* 3.6, H3); 6.67 (1H, dd, *J* 3.4, *J* 1.8, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 146.2 (C3); 123.2 ($CF_3$, $J_{CF}$ 283.9); 91.7 (C5, $^2J$ 33.7); 44.0 (C4). (Isonicotinoyl) $\delta$ 165.3 (C:O); 149.8 (2C, Py); 142.7 (1C, Py); 122.6 (2C, Py). (Furyl) $\delta$ 144.9 (C2); 144.5 (C5); 119.0 (C4); 115.5 (C3). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3153 (OH); 1660 (C=O); 1546, 1494 (C=C). Anal. Calc. for $C_{14}H_{10}F_3N_3O_3$ (325.25): C, 51.70; H, 3.10; N, 12.92%. Found: C, 51.94; H, 3.03; N, 12.88%.

*Data for 3-(2-thienyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-(isonicotinoyl)pyrazole (**7b**)*

Gray crystals (50% yield), mp 156 – 158 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.49 (1H, s, OH); 4.03 (1H, d, *J* 19.0, H4a); 3.66 (1H, d, *J* 19.2, H4b). (Isonicotinoyl) $\delta$ 8.75 (2H, s, Py); 7.62 – 7.58 (2H, m, Py). (Thienyl) $\delta$ 7.75 (1H, dd, *J* 5.2, *J* 1.2, H5); 7.62 – 7.58 (1H, m, H3); 7.18 (1H, dd, *J* 5.1, *J* 3.7, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 149.0 (C3); 123.1 ($CF_3$, $J_{CF}$ 283.7); 92.2 (C5, $^2J$ 33.6); 44.8 (C4). (Isonicotinoyl) $\delta$ 164.8 (C:O); 149.7 (2C, Py); 142.4 (1C, Py); 122.7 (2C, Py). (Thienyl) $\delta$ 132.8 (C2); 131.5 (C3); 130.4 (C5); 128.2 (C4). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3078 (OH); 1652 (C=O); 1551, 1446 (C=C). Anal. Calc. for $C_{14}H_{10}F_3N_3O_2S$ (341.31): C, 49.27; H, 2.95; N, 12.31%. Found: C, 49.28; H, 3.17; N, 12.45%.

*Data for 3-(2-furyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1H-1-(isonicotinoyl)pyrazole (**8a**)*

Gray crystals (65% yield), mp 155 – 157 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.41 (1H, s, OH); 4.01 (1H, d, *J* 19.2 H4a,); 3.72 (1H, d, *J* 19.4, H4b). (Isonicotinoyl) $\delta$ 8.75 (2H, d, *J* 4.2, Py); 7.59 (2H, d, *J* 6.0, Py). (Furyl) $\delta$ 7.84 (1H, s, H5); 7.13 (1H, d, *J* 3.4, H3); 6.65 (1H, dd, *J* 3.4, *J* 1.8, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 146.0 (C3); 103.0 ($CCl_3$); 101.8 (C5); 46.6 (C4). (Isonicotinoyl) $\delta$ 166.7 (C:O); 149.3 (2C, Py); 143.3 (1C, Py); 122.4 (2C, Py). (Furyl) $\delta$ 145.2 (C2); 144.5 (C5); 115.4 (C4); 112.1 (C3). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3288 (OH); 1654 (C=O); 1554, 1482 (C=C). Anal. Calc. for $C_{14}H_{10}Cl_3N_3O_3$ (374,61): C, 44.89; H, 2.69; N, 11.22%. Found: C, 44.59; H, 2.55; N, 11.05%.

*Data for 3-(2-thienyl)-5-hydroxy-5-trichloromethyl-4,5-dihydro-1H-1-(isonicotinoyl)pyrazole (**8b**)*

Gray crystals (60% yield), mp 169 – 171 °C (acetone). $^1$H NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 8.49 (1H, s, OH); 4.11 (1H, d, *J* 19.4, H4a); 3.81 (1H, d, *J* 19.4, H4b). (Isonicotinoyl) $\delta$ 8.74 (2H, d, *J* 5.8, Py); 7.62 – 7.56 (2H, m, Py). (Thienyl) $\delta$ 7.72 (1H, d, *J* 5.0, H5); 7.62 – 7.56 (1H, m, H3); 7.16 (1H, dd, *J* 5.0, *J* 3.6, H4). $^{13}$C NMR (DMSO-$d_6$): (Pyrazole) $\delta$ 149.0 (C3); 102.9 ($CCl_3$); 102.5 (C5); 47.3 (C4). (Isonicotinoyl) $\delta$ 165.4 (C:O); 150.1 (2C, Py); 142.4 (1C, Py); 122.7 (2C, Py). (Thienyl) $\delta$ 132.5 (C2); 131.4 (C3); 130.4 (C5); 128.1 (C4). IR (KBr) $\nu_{max}$ / cm$^{-1}$: 3231 (OH); 1634(C=O); 1597, 1444 (C=C). Anal. Calc. for $C_{14}H_{10}Cl_3N_3O_2S$ (390.67): C, 43.04; H, 2.58; N, 10.76%. Found: C, 43.33; H, 2.62; N, 10.92%.

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