Regioselective synthesis and antimicrobial evaluation of new 1-aryloxyacetyl-, 1-thiophenoxyacetyl- and 1-phenylaminoacetyl-substituted 3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles

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Abstract

This paper describes an efficient approach for the regioselective synthesis of new series of twenty 1-aryloxy(thio)acetyl and 1-(phenylamino)acetyl-substituted 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles (**3**) in 34–96% yields from the cyclocondensation reaction of 4-alkoxy-4-alkyl-(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones with different substituted acetohydrazides. Dehydration reactions of **3**, carried out in the presence of thionyl chloride, furnished two examples of aromatic 5-trifluoromethyl-1*H*-pyrazole derivatives, in 78–82% yields. From antimicrobial tests the fungi *C. albicans* proved to be particularly susceptible to the action of 1-(phenylamino)acetyl-substituted 3-alkyl-2-pyrazoline derivatives; however the first results are still weak when compared to standard drugs.

Keywords: Pyrazoles, pyrazolines, *N*-phenylglycine, aryloxyacetohydrazides, hydrazides, ketones

Introduction

Pyrazoles, 2-pyrazolines, and their derivatives have a long history of applications in the pharmaceutical and agrochemical industry. Several pyrazoline derivatives, in special, trifluoromethylated ones possess important biological activities in medicinal and agricultural scientific fields as antibacterial, antifungical, antiviral, antitubercular and antitumor agents as well as dyestuffs, analytical reagents and agrochemicals.[1] Some of the pyrazoline derivatives are reported to endue antiinflammatory, anticancer and antidiabetic properties,[2] therefore, they are

useful materials in drug research. In addition, pyrazolines have played a crucial role in the development of theory in heterocyclic chemistry and are also are extensively useful synthons in organic chemistry.[3]

Due to recent launched pharmaceuticals containing perfluoroalkyl substituents, which are more stable to degradation and affect some physical and biological properties, the introduction of a F_3C group into aromatic carbocycles and heterocycles is an important synthetic goal.[4] Among many useful reactions, the introduction of a trifluoromethyl group in organic molecules has received great attention in the literature,[5] where methyl fluorosulfonyl difluoroacetate (MFSDA), as convenient-to-handle liquid reagent, led to a variety of F_3C-containing compounds from aryl, heteroaryl, vinyl, benzyl and allyl halides in good yields and under mild conditions.[6] Recently, trifluoromethyl(1,10-phenanthroline)copper has been employed as an easily handled, thermally stable and also a single component for trifluoromethylation of aryl iodides and bromides in high yield under mild conditions.[7] However, one of the best methods to introduce a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This building block relies on the trifluoroacetylation of enolethers or acetals to give, in one-step and good yields, 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones which have proven to be useful starting materials for the regioselective synthesis of numerous heterocyclic compounds.[8]

On the other hand, the aryloxyacetyl and *N*-phenylglycine derivatives have shown a wide range of biological effects. Among their range of properties, the compounds containing aryloxyacetyl or *N*-phenylglycine scaffold have exhibited fungicidal and bactericidal activities.[9,10] They were also identified as potent anti-inflammatory, analgesic, anticonvulsivant and antiviral agents.[11-13]

However, a review on the literature showed that 5-trifluoromethyl-2-pyrazolines with a substituted acetyl group attached to the 1-position of 2-pyrazoline rings are rare[14] and that bonding to an aryloxy, thioaryloxy or phenylamino groups have not yet been reported.

Driven by the above-mentioned biological properties of trifluoromethyl pyrazolines and aryloxy derivatives and by the fact that there is no report about these two structures assembled together, the aim herein is to describe a facile, efficient and regioselective synthesis of four new series of 5-hydroxy-4,5-dihydro-1*H*-pyrazoles with the introduction of a F_3C group, aryloxy(thio)acetyl and *N*-phenylglycine moieties from the cyclocondensation reaction of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones [$F_3CC(O)CH=CR(OMe/OEt)$, where R = H, alkyl, aryl, heteroaryl] and different substituted-hydrazides to investigate their synthetic procedure, dehydration reactions and possible antimicrobial activity.

Results and Discussion

Synthesis and structure

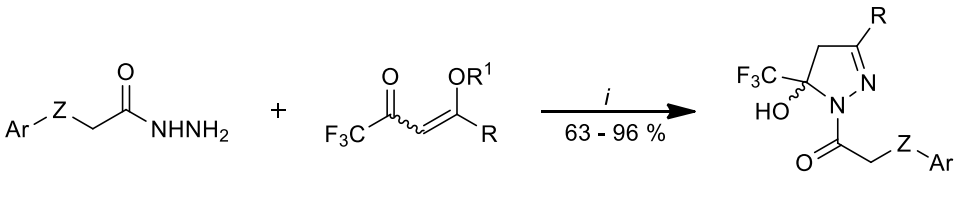
The general synthesis of the 2-aryloxyaceto- and 2-phenylthioacetohydrazides **1a-c** and 2-phenylaminoacetohydrazide (*N*-phenylglycinehydrazide) (**1d**) is described in literature by

refluxing hydrazine monohydrate and the respective ester precursors previously obtained from the reaction of 2-naphthol,[11] phenol,[12] thiophenol,[9] and aniline[10] with ethyl haloacetate in both anhydrous potassium carbonate and acetone at diverse reaction conditions.

Recently, many authors have described the synthesis of bioactive compounds which assemble aryloxy and heterocycle structures such as oxadiazoles, thiadiazoles and triazoles with aryloxy or *N*-methylaniline moieties.[8,10-12] In 2009, Ragavan *et al*.,[9] described the synthesis of some novel of 4-oxy(thio)substituted-1*H*-pyrazol-5(4*H*)-ones through cyclocondensation with *β*-keto esters and hydrazine derivatives. Most of the products were isolated in good yields (38–89%). The findings of this study indicate that almost all of the derivatives showed good inhibition towards bacteria and fungi species screened.

In this context, following our ongoing research interest and the search for new heterocycles with potent biological activity, we decided to investigate whether any synergism might be observed by combining trifluoromethylated pyrazoles, aryloxy(thio)acetyl and *N*-phenylglycine derivatives, to produce a new class of possible antimicrobial agents. In the present work, we report our results on the synthesis and antimicrobial screening of novel 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles, as well as their dehydration reaction aiming to isolate examples of the aromatic pyrazole rings.

The new series of 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles 1-(2-naphthoxyacetyl)-, 1-phenoxyacetyl-, 1-thiophenoxyacetyl- and 1-(phenylamino)acetyl-substituted derivatives **3aa-3de** were synthesized from the cyclocondensation reaction of 4-alkoxy-4-alkyl-(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones **2a-e** previously synthesized,[15] with 2-(aryloxy)aceto-, 2-(phenylthio)aceto- and 2-(phenylamino)acetohydrazides **1a-d**, at a molar ratio 1:1, under reflux of methanol. This method furnished air-stable products in 34–96% yields (Scheme 1).



1a-d **2a-e** **3aa-3de**
20 examples **(3 ArZ/R)**

1,3	**a**	**b**	**c**	**d**
ArZ	2-NaphthylO	PhO	PhS	PhNH

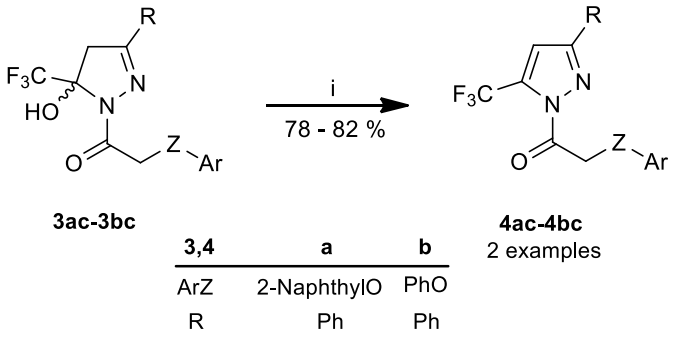
2,3	**a**	**b**	**c**	**d**	**e**
R	H	Me	Ph	2-Furyl	1-Naphthyl
R^1	Et	Me	Me	Me	Me

Scheme 1. Synthetic route for 4,5-dihydropyrazoles **3**. Reagents and conditions: (i) MeOH, reflux, 16 h.

The compounds **1** were synthesized according to a brief review of literature and their structures were assigned from NMR experiments and by comparison with data of other compounds previously described.[9-12]

The reactions to obtain the new compounds **3** were monitored by thin-layer chromatography (TLC) and the optimal temperature and reaction time were under reflux for a period of 16 h. After solvent evaporation, all the products were obtained as colorless, yellow or brown solids by a simple filtration, except for the products **3ca**-**3db** which were isolated as yellow oils. The structures of all compounds **3** synthesized in this work were supported by ^{1}H, ^{13}C {^{1}H} NMR and mass spectrometry (GC-MS) and their purity was proven by Elemental Analyses.

Subsequently, after a review of the literature and attempting to obtain aromatic pyrazoles for further biological assays, we chose thionyl chloride/pyridine as the dehydrating agent and report here the conditions required to accomplish the dehydration of two representative examples of compounds **3** (**3ac** and **3bc**), which present a hydroxyl and a trifluoromethyl group, a aryloxy(thio)acetyl or (phenylamino)acetyl group attached directly to the C-5, C-3, and N-1 atom of the 2-pyrazoline ring, respectively which present an hydroxyl and a trifluoromethyl groups attached directly to the C-5, and an aryloxyacetyl group at the N-1 position of the 2-pyrazoline ring, respectively (Scheme 2). Although, there is a relative difficulty to carry out the dehydration reaction because of the presence of the carbonyl function at position 1 of these two examples of 2-pyrazolines, these compounds underwent dehydration to give the respective 1-(2-naphthoxyacetyl)- and 1-(phenoxyacetyl)-substituted 5-trifluoromethyl-3-phenyl-1*H*-pyrazoles **4ac** and **4bc** in 78–82% yields. The reactions were carried out by stirring the mixtures of **3**, thionyl chloride, and pyridine at 80 °C for about 1 h in benzene as solvent (Scheme 2), according to similar procedures to those described in the literature.[16]



Scheme 2. Synthetic route for aromatic 1*H*-pyrazoles **4**. Reagents and conditions: (i) $SOCl_2$, Pyridine, Benzene, reflux, 1 h.

Compounds **3** showed the ^{1}H NMR chemical shifts of the diastereotopic methylene protons (H-4) of pyrazoline ring as a characteristic AB system with a doublet in average at δ 3.79 and the other doublet at δ 3.48 ppm, respectively with a *geminal* coupling constant of ~19 Hz. The hydroxy protons are shown in the ^{1}H spectra in average at δ 8.14 ppm.

The ^{1}H NMR of the diastereotopic hydrogens of CH_2 group directly bonded to the heteroatoms showed the largest change in chemical shifts. It is known that electronegative atoms such as oxygen, nitrogen and sulfur deshield the hydrogen atoms. The extent of deshielding is proportional to the electronegativity of the heteroatom and its proximity to the hydrogen.[17] This trend has been observed by chemical shifts of diastereotopic hydrogens of CH_2 group obtained in each series: the products **3aa-3ae** and **3ba-3be** (Z = O) showed doublets in average at δ 5.28 and 5.17 ppm for both of them, the products **3ca-3ce** (Z = S) showed one doublet in average at δ 4.16 and the other doublet at δ 4.04 ppm; and the products **3da-3de** (Z = NH) showed doublets in average at δ 4.21 and 4.06 ppm, all of them with a *geminal* coupling constant in average at ~16 Hz. Compounds **3da-3de** also showed a signal for the NH group at ~5.75 ppm.

Compounds **3** present the typical ^{13}C chemical shifts of the pyrazoline ring at δ 150.6 ppm (C-3) and δ 45.4 ppm (C-4). The C-5 shows a characteristic quartet at δ 90.4 ppm with $^2J_{CF}$ = 34 Hz due to the attached F_3C group. The F_3C group shows a typical quartet at δ 122.8 ppm with $^1J_{CF}$ = 286 Hz. The carbonyl carbon showed signal in the range of δ 166.8 ppm.

The heteroatom electronegativity effect observed in ^{13}C NMR was similar to that observed in ^{1}H NMR: compounds **3aa-3ae** and **3ba-3be** (Z = O) showed a signal in the range of δ 155.8 and 157.9 ppm for the C=O and another signal in about of δ 66.1 and 65.9 ppm for CH_2 group, respectively; compounds **3ca-3ce** (Z = S) showed a signal in the range of δ 135.5 ppm for the C=O and another signal at ~36.9 ppm for the CH_2 group; for compounds **3da-3de** (Z = NH), the C=O showed a signal in the range of δ 146.8 ppm and the CH_2 group another signal in average at δ 46.1 ppm.

Compounds **4ac** (ArZ = 2-Naphthyl-O and R = Ph) and **4bc** (ArZ = PhO and R = Ph) presented only relevant distinctions in relation to compounds **3** for the chemical shift of CH_2 group and H-4, C-4 and C-5 of the pyrazoline ring. The ^{1}H NMR showed a singlet for the CH_2 group in δ 5.84 and 4.67 ppm and methylene protons (H-4) of pyrazoline ring as a singlet in δ 7.57 and 6.89 ppm for compounds **4ac** and **4bc**, respectively. In the ^{13}C NMR, C-5 presents a characteristic quartet in average at δ 133.2 ppm with $^2J_{CF}$ = 41 Hz due to the attached F_3C group. The F_3C group shows a typical quartet in average at δ 119.0 ppm with $^1J_{CF}$ = 268 Hz.

Antimicrobial activity

Antimicrobial screens were performed against a panel of microorganisms including bacteria (*Escherichia coli* ATCC 35218, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853), yeast such as fungi (*Candida albicans* ATCC 28367), filamentous fungi (*Aspergillus fumigatus* ATCC 204305), and *Prototheca zopfii* (algae). The antimicrobial activity of each compound was measured by determination of the minimal inhibitory concentration (MIC). The assays were performed by broth microdilution techniques according to CLSI (Clinical Laboratory Standard Institute): M31-A2 (2002)[18] for bacteria, M27-A3(2008)[19] for *C. albicans* and *P. zopfii* and M38-A2 (2008)[20] for filamentous fungi.

The best results were obtained with compounds **3cb**, **3da**, **3db** and **3dc**, which showed poor antifungal activity against *C. albicans*, with MIC equal to 0.31, 0.70, 0.33 and 0.27 µM,

respectively. Once the most notable results were observed for **3da–3dc** series, where Z = NH, we assigned the presence of NH group as the common feature in these compounds as the possible antifungal agent. All results are shown in Table 1.

Table 1. Antimicrobial profile of compounds **3aa-3de**[a]

Entry	Z	R	Gram-positive bacteria	Gram-negative bacteria		Yeast like fungi	Filamentous fungi	Algae
			S. aureus	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. fumigatus*	*P. zopfii*
3aa	O	H	1.18	1.18	2.36	>2.36	>2.36	>2.36
3ab	O	Me	2.27	1.14	1.14	>2.27	2.27	1.14
3ac	O	Ph	>1.93	>1.93	>1.93	>1.93	>1.93	>1.93
3ad	O	2-Furyl	>1.98	>1.98	>1.98	>1.98	>1.98	>1.98
3ae	O	1-Naphthyl	>1.72	>1.72	>1.72	>1.72	>1.72	>1.72
3ba	O	H	1.39	1.39	>2.78	1.39	>2.78	>2.78
3bb	O	Me	2.65	2.65	2.65	>2.65	1.32	2.65
3bc	O	Ph	>2.20	>2.20	>2.20	>2.20	>2.20	>2.20
3bd	O	2-Furyl	2.26	2.26	1.13	1.13	1.13	1.13
3be	O	1-Naphthyl	1.93	>1.93	>1.93	>1.93	>1.93	>1.93
3ca	S	H	1.31	>2.63	>2.63	1.31	>2.63	2.63
3cb	S	Me	1.26	1.26	1.26	**0.31**	1.26	2.51
3cc	S	Ph	>2.10	>2.10	>2.10	1.05	2.10	2.10
3cd	S	2-Furyl	>2.16	>2.16	>2.16	1.08	>2.16	2.16
3ce	S	1-Naphthyl	>1.86	>1.86	>1.86	0.93	1.86	1.86
3da	NH	H	1.39	1.39	>2.79	**0.70**	>2.79	2.79
3db	NH	Me	1.33	1.33	>2.66	**0.33**	>2.66	2.66
3dc	NH	Ph	1.10	1.10	1.10	**0.27**	2.20	2.20
3dd	NH	2-Furyl	>2.27	1.13	1.13	1.13	1.13	2.27
3de	NH	1-Naphthyl	0.97	0.97	0.97	0.97	0.97	1.94
A	-	-	0.0002	0.0067	0.0002	-	-	-
B	-	-	-	-	-	0.0131	-	-
C	-	-	-	-	-	-	0.001	0.0005

A = Imipenem; B = Fluconazole; C = Amphotericin B. [a]MIC (triplicates) expressed in μM.

Conclusions

To summarize, in this study we showed a method to obtain new series of 1,3,5,5-tetra-substituted 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles with introduction of 1-(2-naphthoxyacetyl)-, 1-phenoxyacetyl-, 1-thiophenoxyacetyl- and 1-(phenylamino)acetyl moieties in a one-step reaction. This regioselective method furnished air-stable products in very good yields.

We also evaluated the antimicrobial profile of these new compounds. Of the microorganisms tested, *C. albicans* proved to be particularly susceptible to the action of compounds **3da, 3db** and **3dc**. We assigned these results to the presence of NH group as possible responsible for the antifungal activity. However, these results are negligible when comparisons are done with standard drugs. In addition, further studies are needed to increase these results, once several other substituents can be attached to positions 3 and 4 of pyrazoline ring.

Experimental Section

General. Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200/400 spectrometer 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in DMSO-d_6 and $CDCl_3$ using TMS as internal reference. The GC was equipped with a split–splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and the helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

Synthesis

The 2-(aryloxy)aceto-, 2-(phenylthio)aceto- and 2-(phenylamino)acetohydrazides **1a-d** were obtained by the method reported in previous publication and had their molecular structure, ^{1}H and ^{13}C {^{1}H} NMR data and melting points compared with the available literature.[9-12]

4-Alkoxy-4-alkyl-(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones **2** were prepared according to the previous publication[14] from the trifluoroacetylation reaction of the respective enolethers **2a-b** or acetals **2c-e** with trifluoroacetic anhydride in the presence of pyridine. The pure compounds **2** were obtained by distillation under reduced pressure in agreement with the literature data.[15]

General procedure for synthesis of 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles 1-(2-naphthoxyacetyl)-, 1-phenoxyacetyl-, 1-thiophenoxy-acetyl-, 1-(phenylamino)acetyl derivatives (3aa-3de)

To a stirred mixture of the respective hydrazide **1a-d** (2 mmol) in MeOH (15 mL), the corresponding 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones **2a-e** (2 mmol)

was added. The mixture was stirred under reflux for 16 h. After this time, the solvent was evaporated and the products were obtained regioselectively as colorless, yellow or brown air-stable products. Compounds **3** presented a high degree of purity and did not undergo recrystallization.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-(2-naphthoxyacetyl)pyrazole (3aa). Yellow solid; yield 65%; mp 119-121 ºC. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ = 7.79 (s, 1H, OH), 7.75 (s, 1H, H-3), 7.73-7.69 (m, 1H, Ar), 7.47-7.24 (m, 4H Ar), 7.11-7.06 (m, 2H, Ar), 5.18 (d, 1H, CH_2, Ha, J = 16.4), 5.07 (d, 1H, CH_2, Hb, J = 16.4), 3.40 (d, 1H, H-4a, J = 19.3), 3.21 (d, 1H, H-4b, J = 19.3). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 169.4 (C=O), 155.7 (C-O), 146.1 (C-3), 134.2, 129.7, 129.4, 127.6, 126.8, 126.5, 124.1, 118.5, 107.2 (9C, Ar), 122.8 (q, ^1J = 286.1, F_3C), 90.2 (q, ^2J = 34.3, C-5), 65.9 (CH_2), 44.5 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 339 (M+, 50), 185 (100), 145 (62). Anal. Calc. for $C_{16}H_{13}F_3N_2O_3$ (338.14): C, 56.81; H, 3.87; N, 8.28. Found: C, 56.70; H, 3.83; N, 8.31.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-methyl-1*H*-1-(2-naphthoxyacetyl)pyrazole (3ab). Brown solid; yield 63%; mp 152-154 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.85 (s, 1H, OH), 7.82 (d, 2H, Ar, J = 7.8), 7.74 (d, 1H, Ar, J = 8.1), 7.44 (t, 1H, Ar, J = 7.8), 7.34 (t, 1H, Ar, J = 7.8), 7.21-7.19 (m, 2H, Ar), 5.13 (d, 1H, CH_2, Ha, J = 16.4), 5.04 (d, 1H, CH_2, Hb, J = 16.4), 3.46 (d, 1H, H-4a, J = 19.4), 3.11 (d, 1H, H-4b, J = 19.4), 2.06 (s, 3H, Me). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165.0 (C=O), 155.7 (C-3), 154.7 (C-O), 133.8, 128.9, 128.5, 127.2, 126.4, 126.1, 123.4, 118.1, 107.2 (9C, Ar), 122.9 (q, ^1J = 286.1, F_3C), 90.5 (q, ^2J = 34.4, C-5), 66.0 (CH_2), 47.4 (C-4), 14.9 (Me). GC–MS (EI, 70 eV): *m/z* (%) = 352 (M+, 100), 181 (32), 144 (96). Anal. Calc. for $C_{17}H_{15}F_3N_2O_3$ (352.16): C, 57.96; H, 4.29; N, 7.95. Found: C, 57.89; H, 4.32; N, 7.91.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-phenyl-1*H*-1-(2-naphthoxyacetyl)pyrazole (3ac). Colorless solid; yield 63%; mp 128-130 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 8.30 (s, 1H, OH), 7.91-7.83 (m, 4H, Ar), 7.77 (d, 1H, Ar, J = 7.9), 7.54-7.50 (m, 3H, Ar), 7.46-7.32 (m, 2H, Ar), 7.28-7.23 (m, 2H, Ar), 5.36 (d, 1H, CH_2, Ha, J = 16.4), 5.24 (d, 1H, CH_2, Hb, J = 16.4), 3.97 (d, 1H, H-4a, J = 19.4), 3.62 (d, 1H, H-4b, J = 19.4). ^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 165.6 (C=O), 155.8 (C-O), 152.7 (C-3), 134.0, 130.9, 129.9, 129.3, 128.8, 128.6, 127.4, 126.8, 126.6, 126.4, 123.7, 118.5, 107.2 (15C, Ar), 123.0 (q, ^1J = 286.1, F_3C), 91.2 (q, ^2J = 34.3, C-5), 66.1 (CH_2), 44.1 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 414 (M+, 100), 212 (31), 145 (72). Anal. Calc. for $C_{22}H_{17}F_3N_2O_3.H_2O$ (414.38): C, 61.11; H, 4.43; N, 6.48. Found: C, 61.45; H, 4.16; N, 6.59.

5-Trifluoromethyl-3-(2-furyl)-5-hydroxy-4,5-dihydro-1*H*-1-(2-naphthoxyacetyl)pyrazole (3ad). Brown solid; 66%; 157-159 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 8.34 (s, 1H, OH), 7.97 (s, 1H, furyl), 7.85 (d, 2H, Ar, J = 7.9), 7.76 (d, 1H, Ar, J = 8.1), 7.49-7.31 (m, 2H, Ar), 7.25 (s, 1H, Ar), 7.21 (s, 1H, furyl), 7.16 (d, 1H, Ar, J = 8.2), 6.72 (s, 1H, furyl), 5.28 (d, 1H, CH_2, Ha, J = 16.4), 5.15 (d, 1H, CH_2, Hb, J = 16.4), 3.87 (d, 1H, H-4a, J = 19.4), 3.51 (d, 1H, H-4b, J = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165.7 (C=O), 155.9 (C-O), 146.2 (C-3), 145.0, 144.2 (2C, furyl), 134.1, 129.4, 128.7, 127.5, 126.7, 126.5, 123.8, 118.5, 107.3 (9C, Ar), 115.3, 112.4 (2C, furyl), 123.0 (q, ^1J = 285.9, F_3C), 91.2 (q, ^2J = 34.3, C-5), 66.2 (CH_2), 43.9 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 404 (M+, 100), 233 (66), 145 (56). Anal. Calc. for $C_{20}H_{15}F_3N_2O_4.H_2O$ (404.31): C, 56.87; H, 4.06; N, 6.93. Found: C, 56.90; H, 3.93; N, 6.73.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-(1-naphthyl)-1*H*-1-(2-naphthoxyacetyl)pyrazole (3ae). Colorless solid; yield 96%; mp 174-175 ºC. ^{1}H NMR (200.13 MHz, DMSO-d_6): δ = 9.17 (d, 1H, Ar, J = 8.1), 8.35 (s, 1H, OH), 8.13-8.03 (m, 2H, Ar), 7.96-7.84 (m, 3H, Ar), 7.76 (d, 1H, Ar, J = 8.1), 7.69-7.59 (m, 3H, Ar), 7.50-7.36 (m, 2H, Ar), 7.28 (d, 2H, Ar, J = 7.9), 5.43 (d, 1H, CH_2, Ha, J = 16.4), 5.34 (d, 1H, CH_2, Hb, J = 16.3), 4.21 (d, 1H, H-4a, J = 19.3), 3.81 (d, 1H, H-4b, J = 19.3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165.6 (C=O), 155.8 (C-O), 152.9 (C-3), 133.8, 133.4, 131.2, 129.5, 129.2, 129.1, 128.5, 127.6, 127.2, 126.4, 126.1, 125.9, 124.8, 123.4, 118.1, 107.3 (19C, Ar), 120.1 (q, ^1J = 286.1, F_3C), 90.1 (q, ^2J = 34.3, C-5), 66.4 (CH_2), 46.3 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 414 (M+, 63), 262 (100). Anal. Calc. for $C_{26}H_{19}F_3N_2O_3$ (464.41): C, 67.24; H, 4.12; N, 6.03. Found: C, 67.30; H, 4.11; N, 6.19.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-(phenoxyacetyl)pyrazole (3ba). Yellow solid; yield 67%; mp 89-91 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.92 (s, 1H, OH), 7.03 (s, 1H, 1H-3), 7.27 (t, 2H, Ar, J = 7.9), 6.94 (t, 1H, Ar, J = 7.8), 6.88 (d, 2H, Ar, J = 8.1), 5.04 (d, 1H, CH_2, Ha, J = 16.3), 4.94 (d, 1H, CH_2, Hb, J = 16.3), 3.43 (d, 1H, H-4a, J = 19.4), 3.12 (d, 1H, H-4b, J = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165.7 (C=O), 157.9 (C-O), 145.8 (C-3), 129.1, 120.7, 114.2 (5C, Ar), 122.9 (q, ^1J = 285.9, F_3C), 89.0 (q, ^2J = 34.3, C-5), 65.9 (CH_2), 45.5 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 288 (M+, 100), 167 (82), 107 (25), 77 (41). Anal. Calc. for $C_{12}H_{11}F_3N_2O_3$ (288.07): C, 50.01; H, 3.85; N, 9.72. Found: C, 50.01; H, 3.99; N, 9.63.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-methyl-1*H*-1-(phenoxyacetyl)pyrazole (3bb). Yellow solid; yield 63%; mp 55-57 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.85 (s, 1H, OH), 7.26 (t, 1H, Ar, J = 7.9), 6.93 (t, 1H, Ar, J = 7.8), 6.87 (d, 1H, Ar, J = 8.1), 4.99 (d, 1H, CH_2, Ha, J = 16.4), 4.91 (d, 1H, CH_2, Hb, J = 16.4), 3.43 (d, 1H, H-4a, J = 19.4), 3.07 (d, 1H, H-4b, J = 19.4), 2.03 (s, 3H, Me). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165.2 (C=O), 157.9 (C-3), 154.6 (C-O), 129.1, 120.6, 114.3 (5C, Ar), 122.9 (q, ^1J = 285.8, F_3C), 90.4 (q, ^2J = 33.3, C-5), 65.8 (CH_2), 47.4 (C-4), 14.9 (Me). GC–MS (EI, 70 eV): *m/z* (%) = 302 (M+, 60), 181 (100), 107 (21), 77 (43). Anal. Calc. for $C_{13}H_{13}F_3N_2O_3$ (302.09): C, 51.66; H, 4.34; N, 9.27. Found: C, 51.80; H, 4.39; N, 9.25.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-phenyl-1*H*-1-(phenoxyacetyl)pyrazole (3bc). Colorless solid; yield 75%; mp 100-102 ºC. ^{1}H NMR (200.13 MHz, DMSO-d_6): δ = 8.07 (s, 1H, OH), 7.83 (d, 2H, Ar, J = 8.2), 7.50 (s, 3H, Ar), 7.28 (t, 2H, Ar, J = 7.9), 6.94 (d, 3H, Ar, J = 8.1), 5.18 (d, 1H, CH_2, Ha, J = 16.3), 5.09 (d, 1H, CH_2, Hb, J = 16.4), 3.89 (d, 1H, H-4a, J = 19.4), 3.57 (d, 1H, H-4b, J = 19.3). ^{13}C NMR (50.32 MHz, DMSO-d_6): δ = 165.8 (C=O), 157.9 (C-O), 152.6 (C-3), 130.8, 129.8, 129.3, 128.7, 126.7, 120.8, 114.5 (9C, Ar), 123.0 (q, ^1J = 286.2, F_3C), 91.2 (q, ^2J = 33.3, C-5), 66.0 (CH_2), 44.0 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 364 (M+, 85), 243 (100), 104 (15), 77 (39). Anal. Calc. for $C_{18}H_{15}F_3N_2O_3$ (364.32): C, 59.34; H, 4.15; N, 7.69. Found: C, 59.12, H, 4.32, N, 7.67.

5-Trifluoromethyl-3-(2-furyl)-5-hydroxy-4,5-dihydro-1*H*-1-(phenoxyacetyl)pyrazole (3bd). Brown solid; 63%; 99-101 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 8.19 (s, 1H, OH), 7.78 (d, 1H, furyl, J = 4.3), 7.58 (d, 2H, furyl, J = 4.5), 7.28 (t, 2H, Ar, J = 7.9), 7.20-7.18 (m, 1H, furyl), 6.96 (d, 1H, Ar, J = 8.1), 6.91 (d, 2H, Ar, J = 8.1), 5.10 (d, 1H, CH_2, Ha, J = 16.4), 5.00 (d, 1H, CH_2, Hb, J = 16.3), 3.92 (d, 1H, H-4a, J = 19.3), 3.57 (d, 1H, H-4b, J = 19.3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165.5 (C=O), 157.9 (C-O), 148.6 (C-3), 132.7, 131.3, 130.3 (3C, furyl), 129.3 (2C, Ar), 128.1 (furyl), 120.8, 114.5 (3C, Ar), 122.9 (q, ^1J = 285.9, F_3C), 91.2 (q, ^2J = 33.9, C-5), 65.9 (CH_2), 44.6 (C-4). GC–MS (EI, 70 eV): *m/z*

(%) = 354 (M+, 40), 233 (100), 107 (18), 77 (39). Anal. Calc. for $C_{16}H_{13}F_3N_2O_4$ (354.28): C, 54.24; H, 3.70; N, 7.91. Found: C, 54.01, H, 3.73, N, 8.08.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-(1-naphthyl)-1*H*-1-(phenoxyacetyl)pyrazole (3be). Colorless solid; yield 88%; mp 118-120 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 9.07 (d, 1H, Ar, J = 8.1), 8.17 (s, 1H, OH), 8.07 (d, 1H, Ar, J = 8.2), 8.02 (d, 1H, Ar, J = 8.1), 7,89 (d, 1H, Ar, J = 8.1), 7.65 (t, 1H, Ar, J = 7.8), 7.60 (t, 2H, Ar, J = 7.9), 7.30 (t, 2H, Ar, J = 7.9), 6.96 (m, 3H, Ar,); 5.27 (d, 1H, CH_2, Ha, ^2J = 16.3), 5.17 (d, 1H, CH_2, Hb, ^2J = 16.4), 4.12 (d, 1H, H-4a, ^2J = 19.3), 3.77 (d, 1H, H-4b, ^2J = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 165,7 (C=O), 157.9 (C-O), 152.8 (C-3), 133.4, 131.2, 129.5, 129.2, 129.1, 128.5, 127.6, 126.1, 125.9, 125.8, 124.8, 120.7, 114.4 (15C, Ar), 122.9 (q, ^1J = 286.2, F_3C), 90.0 (q, ^2J = 34.4, C-5), 66.3 (CH_2), 46.3 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 414 (M+, 92), 293 (100), 153 (37), 77 (35). Anal. Calc. for $C_{22}H_{17}F_3N_2O_3$ (414.38): C, 63.77; H, 4.14; N, 6.76. Found: C, 63.48; H, 4.37; N, 7.30.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-(thiophenoxyacetyl)pyrazole (3ca). Yellow oil; yield 65%. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.82 (s, 1H, OH), 7.39 (s, 1H, Ar), 7.37 (s, 1H, H-3), 7.30 (t, 2H, Ar, J = 7.9), 7.20 (t, 2H, Ar, J = 7.9), 4.13 (d, 1H, CH_2, Ha, J = 16.4), 4.06 (d, 1H, CH_2, Hb, J = 16.4), 3.43 (d, 1H, H-4a, J = 19.4), 3.14 (d, 1H, H-4b, J = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 166.5 (C=O), 145.0 (C-3), 135.4 (C-S), 128.5, 128.4, 125.8 (5C, Ar), 122.8 (q, ^1J = 285.9, F_3C), 88.9 (q, ^2J = 34.3, C-5), 45.7 (C-4), 36.8 (CH_2). GC–MS (EI, 70 eV): *m/z* (%) = 304 (M+, 100), 150 (61), 128 (98), 109 (15). Anal. Calc. for $C_{12}H_{11}F_3N_2O_2S$ (304.29): C, 47.37; H, 3.64; N, 9.21; S, 10.54. Found: C, 47.20; H, 3.81; N, 9.34; S, 10.44.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-methyl-1*H*-1-(thiophenoxyacetyl)pyrazole (3cb). Yellow oil; yield 67%. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.70 (s, 1H, OH), 7.38 (d, 2H, Ar, J = 8.1), 7.30 (t, 2H, Ar, J = 7.8), 7.20 (t, 1H, Ar, J = 7.7), 4.08 (d, 1H, CH_2, Ha, J = 16.3), 4.02 (d, 1H, CH_2, Hb, J = 16.3), 3.41 (d, 1H, H-4a, J = 19.4), 3.07 (d, 1H, H-4b, J = 19.3), 1.99 (s, 3H, Me). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 166.1 (C=O), 154.0 (C-3), 135.6 (C-S), 128.6, 128.4, 125.9 (5C, Ar), 123.0 (q, ^1J = 286.3, F_3C), 90.4 (q, ^2J = 34.4, C-5), 47.7 (C-4), 36.9 (CH_2), 14.9 (Me). GC–MS (EI, 70 eV): *m/z* (%) = 318 (M+, 100), 150 (76), 123 (75), 109 (13). Anal. Calc. for $C_{13}H_{13}F_3N_2O_2S$ (318.31): C, 49.05; H, 4.12; N, 8.80; S, 10.07. Found: C, 48.96; H, 4.18; N, 8.92; S, 9.98.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-phenyl-1*H*-1-(thiophenoxyacetyl)pyrazole (3cc). Colorless solid; yield 86%; mp 81-83 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.98 (s, 1H, OH), 7.76 (d, 2H, Ar, J = 8.3), 7.48 (d, 3H, Ar, J = 8.1), 7.42 (d, 2H, Ar, J = 8.3), 7.30 (t, 2H, Ar, J = 7.9), 7,20 (t, 1H, Ar, J = 7.8), 4.27 (d, 1H, CH_2, Ha, J = 16.4), 4.23 (d, 1H, CH_2, Hb, J = 16.4), 3.88 (d, 1H, H-4a, J = 19.4), 3.57 (d, 1H, H-4b, J = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 166.5 (C=O), 151.6 (C-3), 135.5 (C-S), 130.5, 129.8, 128.7, 128.5, 128.5, 126.4, 126.0 (10C, Ar); 122.9 (q, ^1J = 286.3, F_3C), 91.0 (q, ^2J = 34.4, C-5), 44.2 (C-4), 36.9 (CH_2). GC–MS (EI, 70 eV): *m/z* (%) = 380 (M+, 100), 230 (74), 150 (87), 123 (65). Anal. Calc. for $C_{18}H_{15}F_3N_2O_2S$ (380.38): C, 56.48; H, 3.97; N, 7.36; S, 8.43. Found: C, 56.69; H, 4.13; N, 7.76; S, 8.23.

5-Trifluoromethyl-3-(2-furyl)-5-hydroxy-4,5-dihydro-1*H*-1-(thiophenoxyacetyl)pyrazole (3cd). Brown solid; yield 57%; mp 92-93 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 8.04 (s, 1H, OH), 7.88 (d, 1H, furyl, J = 4.4), 7.41 (d, 2H, Ar, J = 8.1), 7.30 (t, 2H, Ar, J = 7.9), 7.20 (t, 1H, Ar, J = 7.8), 7.06 (d,

1H, furyl, *J* = 3.4), 6.67-6.66 (m, 1H, furyl), 4.18 (d, 1H, CH_2, Ha, *J* = 16.3), 4.11 (d, 1H, CH_2, Hb, *J* = 16.4), 3.79 (d, 1H, H-4a, *J* = 19.4), 3.47 (d, 1H, H-4b, *J* = 19.3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 166.3 (C=O), 145.7 (C-3), 144.9, 143.1 (2C, furyl), 135.5 (C-S), 128.7, 128.5, 125.9 (5C, Ar), 122.8 (q, ^1J = 285.9, F_3C), 114.4, 112.0 (2C, furyl), 90.6 (q, ^2J = 34.4, C-5), 43.9 (C-4), 36.9 (CH_2). GC–MS (EI, 70 eV): *m/z* (%) = 370 (M+, 70), 220 (100), 151 (36), 123 (28). Anal. Calc. for $C_{16}H_{13}F_3N_2O_3S$ (370.35): C, 51.89; H, 3.54; N, 7.56; S, 8.66. Found: C, 51.81; H, 3.54; N, 7.66; S, 7.97.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-(1-naphthyl)-1*H*-1-(thiophenoxyacetyl)pyrazole (3ce). Colorless solid; yield 76%; mp 141-143 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 9.11-9.09 (m, 1H, Ar), 8.14 (s, 1H, OH), 8.07 (d, 1H, Ar, *J* = 8.1), 8.03-8.00 (m, 1H, Ar), 7.87 (d, 1H, Ar, *J* = 8.1), 7.64-7.58 (m, 3H, Ar), 7.32 (t, 2H, Ar, *J* = 7.9), 7.21 (t, 1H, Ar, *J* = 7.8), 4.38 (d, 1H, CH_2, Ha, *J* = 16.3), 4.26 (d, 1H, CH_2, Hb, *J* = 16.4), 4.12 (d, 1H, H-4a, *J* = 19.4), 3.80 (d, 1H, H-4b, *J* = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 166.5 (C=O), 152.2 (C-3), 135.5 (C-S), 133.4, 131.1, 129.5, 129.1, 128.7, 128.5, 128.5, 127.4, 126.1, 126.0, 126.0, 126.0, 124.8 (15C, Ar), 123.0 (q, ^1J = 286.3, F_3C), 90.0 (q, ^2J = 34.4, C-5), 46.6 (C-4), 37.2 (CH_2). GC–MS (EI, 70 eV): *m/z* (%) = 430 (M+, 65), 280 (100), 153 (27), 123 (27). Anal. Calc. for $C_{22}H_{17}F_3N_2O_2S$ (430.44): C, 61.93; H, 3.98; N, 6.51; S, 7.45. Found: C, 61.46; H, 4.02; N, 6.88; S, 7.32.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-(phenylaminoacetyl)pyrazole (3da). Yellow oil; yield 56%. ^{1}H NMR (200.13 MHz, DMSO-d_6): δ = 7.74 (s, 1H, OH), 7.25 (s, 1H, H-3), 7.07 (t, 3H, Ar, *J* = 7.7), 6.58 (d, 2H, Ar, *J* = 8.1), 5.65 (s, 1H, NH), 4.18 (d, 1H, CH_2, Ha, *J* = 16.3), 4.08 (d, 1H, CH_2, Hb, *J* = 16.3), 3.40 (d, 1H, H-4a, *J* = 19.3), 3.12 (d, 1H, H-4b, *J* = 19.3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 168.3 (C=O), 147.9 (C-3), 145.1 (C-NH), 128.4, 116.0, 111.1 (5C, Ar), 123.0 (q, ^1J = 285.9, F_3C), 89.1 (q, ^2J = 33.9, C-5), 45.8 (CH_2), 45.5 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 287 (M+, 20), 106 (100), 77 (26), 51 (8). Anal. Calc. for $C_{12}H_{12}F_3N_3O_2$ (287.24): C, 50.18; H, 4.21; N, 14.63. Found: C, 50.32; H, 4.03; N, 14.50.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-methyl-1*H*-1-(phenylaminoacetyl)pyrazole (3db). Yellow oil; yield 68%. ^{1}H NMR (200.13 MHz, DMSO-d_6): δ = 7.66 (s, 1H, OH), 7.06 (t, 2H, Ar, *J* = 7.9), 6.57 (d, 3H, Ar, *J* = 8.1), 5.70 (s, 1H, NH), 4.14 (d, 1H, CH_2, Ha, *J* = 16.3), 4.04 (d, 1H, CH_2, Hb, *J* = 16.4), 3.41 (d, 1H, H-4a, *J* = 19.4), 3.05 (d, 1H, H-4b, *J* = 19.4), 2.04 (s, 3H, Me). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 171.3 (C=O), 155.8 (C-3), 147.1 (C-NH), 129.3, 118.0, 113.1 (5C, Ar), 123.0 (q, ^1J = 286.3, F_3C), 91.4 (q, ^2J = 34.2, C-5), 46.7 (CH_2), 46.5 (C-4), 15.6 (Me). GC–MS (EI, 70 eV): *m/z* (%) = 301 (M+, 87), 106 (100), 77 (28), 51 (8). Anal. Calc. for $C_{13}H_{14}F_3N_3O_2$ (301.26): C, 51.83; H, 4.68; N, 13.95. Found: C, 51.64; H, 4.78; N, 14.25.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-phenyl-1*H*-1-(phenylaminoacetyl)pyrazole (3dc). Colorless solid; yield 91%; mp 127-129 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.98 (s, 1H, OH), 7.86-7.84 (m, 2H, Ar), 7.51-7.47 (m, 3H, Ar), 7.08 (t, 2H, Ar, *J* = 7.8), 6.62 (d, 2H, Ar, *J* = 8.1), 6.57 (t, 1H, Ar, *J* = 7.8), 5.67 (s, 1H, NH), 4.32 (d, 1H, CH_2, Ha, *J* = 16.3), 4.24 (d, 1H, CH_2, Hb, *J* = 16.3), 3.88 (d, 1H, H-4a, *J* = 19.4), 3.56 (d, 1H, H-4b, *J* = 19.3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 168.2 (C=O), 151.8 (C-3), 147.9 (C-NH), 130.4; 129.9, 128.4, 126.4, 126.7, 116.0, 112.2 (9C, Ar), 122.9 (q, ^1J = 285.9, F_3C), 91.0 (q, ^2J = 34.3, C-5), 45.9 (CH_2), 43.9 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 363 (M+,

28), 106 (100), 77 (23), 51 (4). Anal. Calc. for $C_{18}H_{16}F_3N_3O_2$ (363.33): C, 59.50, H, 4.44, N, 11.57. Found: C, 59.47, H, 4.53, N, 11.47.

5-Trifluoromethyl-3-(2-furyl)-5-hydroxy-4,5-dihydro-1*H*-1-(phenylaminoacetyl)pyrazole (3dd). Brown solid; yield 40%; mp 121-122 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 8.13 (s, 1H, OH), 7.93 (d, 1H, furyl, J = 2.6), 7.11 (d, 1H, furyl, J = 4.3), 7.08 (t, 2H, Ar, J = 7.8), 6.70-6.69 (m, 1H, furyl), 6.59 (s, 1H, Ar), 6.56 (t, 2H, Ar, J = 7.8), 5.77 (t, 1H, NH, J = 6.2), 4.24 (dd, 1H, CH_2, Ha, J = 16.4, $J_{H\text{-}NH}$ = 11.6), 4.17 (dd, 1H, CH_2, Hb, J = 16.4, $J_{H\text{-}NH}$ = 11.4), 3.80 (d, 1H, H-4a, J = 19.4), 3.46 (d, 1H, H-4b, J = 19.3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 168.3 (C=O), 148.3 (C-3), 146.0 (C-NH), 145.1, 143.5 (2C, furyl), 128.8, 116.1 (3C, Ar), 115.0, 112.3 (2C, furyl), 112.2 (2C, Ar), 123.2 (q, ^1J = 286.2, F_3C), 90.7 (q, ^2J = 34.3, C-5), 45.9 (CH_2), 43.9(C-4). GC–MS (EI, 70 eV): *m/z* (%) = 354 (M+, 39), 233 (100), 107 (17), 77 (38), 51 (8). Anal. Calc. for $C_{16}H_{14}F_3N_3O_3$ (353.30): C, 54.39; H, 3.99; N, 11.89. Found: C, 54.35; H, 4.02; N, 12.07.

5-Trifluoromethyl-5-hydroxy-4,5-dihydro-3-(1-naphthyl)-1*H*-1-(phenylaminoacetyl)pyrazole (3de). Colorless solid; yield 34%; mp 157-158 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 9.18 (d, 1H, Ar, J = 8.1), 8.23 (s, 1H, OH), 8.08 (t, 2H, Ar, J = 7.9), 7.92 (d, 1H, Ar, J = 8.2), 7.78-7.58 (m, 3H, Ar); 7.10 (t, 2H, Ar, J = 7.9), 6.66-6.45(m, 3H, Ar), 5.98 (t, 1H, NH, J = 6.3), 4.45 (dd, 1H, CH_2, Ha, J = 16.3, $J_{H\text{-}NH}$ = 11.4), 4.35 (dd, 1H, CH_2, Hb, J = 16.3, $J_{H\text{-}NH}$ = 11.5), 4.15 (d, 1H, H-4a, J = 19.4), 3.76 (d, 1H, H-4b, J = 19.4). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 168.4 (C=O), 152.4 (C-3), 148.1 (C-NH), 133.4, 131.1, 129.5, 129.1, 128.5, 127.6, 126.1, 125.7, 124.9, 116.1, 112.1 (15C, Ar), 123.0 (q, ^1J = 285.9, F_3C), 90.0 (q, ^2J = 34.3, C-5), 46.4 (CH_2), 46.1 (C-4). GC–MS (EI, 70 eV): *m/z* (%) = 413 (M+, 38), 106 (100), 77 (8). Anal. Calc. for $C_{22}H_{18}F_3N_3O_2$ (413.39): C, 63.92, H, 4.39, N, 10.16. Found: C, 63.86, H, 4.41, N, 10.39.

General procedure for the synthesis of 1-(2-naphthoxyacetyl)- and 1-(phenoxyacetyl)-substituted 5-trifluoromethyl-3-phenyl-1*H*-pyrazoles (4ac-4bc)

A solution of 5-trifluoro-methyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (**4ac**, **4bc**) (2.6 mmol) and pyridine (33.8 mmol, 3 mL) in benzene (50 mL) was cooled to 0 °C and thionyl chloride (16.8 mmol, 1.22 mL) diluted in benzene (25 mL) was added dropwise over 10 min. The solution was stirred for an additional 30 min, during which time the temperature was allowed to rise to 20 °C. The mixture was then heated under reflux (bath temperature 80 °C) for 1 h and then filtered to remove the pyridine hydrochloride at room temperature. The solution was extracted twice with benzene (2 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure by rotatory evaporator left **4ac** and **4bc** as solid products, which were purified by recrystallization from aqueous ethanol.

5-Trifluoromethyl-3-phenyl-1*H*-1-(2-naphthoxyacetyl)pyrazole (4ac). Brown solid; yield 82%; mp 146-148 °C. ^{1}H NMR (200.13 MHz, DMSO-d_6): δ = 8.11 (d, 2H, Ar, J = 8.3), 8.03 (s, 1H, Ar), 7.91-7.81 (m, 3H, Ar), 7.55 (d, 3H, Ar, J = 8.1), 7.54 (s, 1H, H-4), 7.47-7.30 (m, 3H, Ar), 5.85 (s, 2H, CH_2). ^{13}C NMR (50.32 MHz, DMSO-d_6): δ =166.0 (C=O), 155.4 (C-O), 153.1 (C-3), 134.0, 130.1, 129.7, 129.4, 129.0, 128.8, 128.2, 127.4, 127.2, 126.7, 126.4, 123.9, 118.3, 107.4 (15C, Ar), 133.4 (q, ^2J = 41.5, C-5), 119.1 (q, ^1J = 268.4, F_3C), 112.1 (C-4), 66.2 (CH_2). GC–MS (EI, 70 eV): *m/z* (%) = 396 (M+, 100), 225

(84), 77 (13). Anal. Calc. for $C_{22}H_{17}F_3N_2O_2$ (396.38): C, 66.33, H, 4.30, N, 7.03. Found: C, 66.45, H, 4.02, N, 6.85.

5-Trifluoromethyl-3-phenyl-1*H*-1-(phenoxyacetyl)pyrazole (4bc). Yellow solid; yield 78%; mp 125-127 °C. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.87-7.82 (m, 2H, Ar), 7.55-7.42 (m, 3H, Ar), 7.34-7.22 (m, 3H, Ar), 6.99-6.89 (m, 2H, Ar), 6.93 (s, 1H, H-4), 4.68 (s, 2H, CH_2). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ =165.9 (C=O), 157.4 (C-O), 152.9 (C-3), 129.8, 129.5, 129.2, 128.7, 126.2, 121.1, 114.6 (9C, Ar), 133.1 (q, ^2J = 41.4, C-5), 118.9 (q, ^1J = 268.4, F_3C), 111.9 (C-4), 66.0 (CH_2). GC–MS (EI, 70 eV): *m/z* (%) = 346 (M+, 44), 225 (100), 77 (41). Anal. Calc. for $C_{18}H_{15}F_3N_2O_2$ (346.32): C, 62.07, H, 4.34, N, 8.04. Found: C, 62.30, H, 4.14, N, 8.03.

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