Asian Journal of Chemistry; Vol. 28, No. 6 (2016), 1351-1360

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19703

Synthesis, Characterization and Keto-Enol Tautomerism of Novel 2-(Trifluoromethyl)benzohydrazide Derivatives

RAMESH NAVUDU, GANGADHARA RAO MANNEM and HARI BABU BOLLIKOLLA*

Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar-522 510, India

*Corresponding author: Tel: +91 863 2346575; E-mail: dr.b.haribabu@gmail.com

Received: 30 October 2015; *Accepted*: 29 January 2016; *Published online*: 29 February 2016; AJC-17807

A series of novel 2-(trifluoromethyl)benzohydrazide derivatives were synthesized starting from 2,2,2-trifluoromethyl benzoic acid in three consecutive steps by using hydrazine hydride and aldehydes at room temperature. In above methodology a total of 21 novel benzohydrazide derivatives (**4a-4u**) were produced. The proton NMR spectra revealed that all the 2-(trifluoromethyl)benzohydrazide derivatives were showed keto-enol tautomerism. An observation on the keto-enol ratios of various substituents, provided that compounds having electron withdrawing groups gives high enol form compared to the donating groups.

Keywords: 2,2,2-Trifluoromethyl benzoic acid, Arylaldehydes, Benzohydrazide derivatives, Keto-enol tautomerism.

INTRODUCTION

Hydrazides and hydrazones are the important type of intermediates and can be easily converted into biologically active compounds [1]. The present aimed compounds are the main constituents in some potent drugs possessing an azomethine moiety -NHN=CH-; they have versatile biological activities such as antibacterial (Gram-positive and Gram-negative) [2-7], anti-HIV [8], antifungal [9], antioxidant [10-13], anti-inflammatory [14,15], antimalarial [16], anticonvulsant [17], antidepressant [18], anticancer [19-21], antibiotic [22] and anesthetic [23] activities. So hydrazones and their derivatives have significant importance in novel drug development; insertion of halogen atoms to the molecules will enhance the activity of particular molecule [24]; in particular most of drugs and herbicides contains fluorin, trifluoromethyl and difluoromethyl groups these include as lipid lowering agent atorvastatin [25], TAP's proton inhibitor lansoprazole [26], antidepresent fluoxetine [27], antiprotozoal drug mefloquine [28], *etc*. So insertion of fluorene, fluorinated groups such as trifluoromethane or difluoromethane will enhance the molecule activity. These observations encouraged the development of new trifluoromethyl benzohydrzide derivatives that possess versatile biological activities.

EXPERIMENTAL

Chemicals and solvents are laboratory grade (Merck) and were used as such. The melting points were calculated on Remi melting point apparatus. All reactions were monitored by TLC and all yields refer to isolated products. Proton NMR were recorded in DMSO-d_6 and $CDCl_3$ on Bruker 400 MHz at 400 MHz and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Bruker 400 MHz spectrometer at 100 MHz.

General procedure for preparation of ethyl 2-(trifluoromethyl) benzoate (2): A solution of trifluoromethyl benzoic acid (**1**) (3 mmol) in ethanol (5 mL) and catalytic amount of $SOCl_2$ or H_2SO_4 added at 0 °C then refluxed for 5 h. The reaction was monitored by TLC, after completion of the reaction distilled off the ethanol; poured the reaction mass in to distilled water (50 mL) then extracted with EtOAc (15 mL) twice, ethyl acetate layer was washed with distilled water (15 mL) twice to remove the acid traces then dried over Na_2SO_4 (2 g) distilled off total EtOAc layer.

General procedure for preparation of 2-(trifluoromethyl)benzohydrazide (3): A solution of compound **2** (3 mmol) in 10 mL ethanol and refluxed with 99 % hydrazine hydrate (6 mmol) for 4 h and the reaction was monitored by using TLC after completion. The reaction mass was cooled to room temperature and then poured into 50 mL cold water. The precipitate was filtered off.

General procedure for preparation of (trifluoromethyl)-benzohydrazide derivatives (4a-4u): To a mixture of 2-(trifluoromethyl) (1 mmol) and aromatic aldehyde (1 mmol) in ethanol (5 mL), was added (4 mmol) of 50 % of potassium hydroxide. Stirred the reaction mass for 2-3 h reaction was monitored by TLC. After completion of the reaction the ethanol

was distilled off from the reaction mass, the solid mass poured in to cold water (25 mL) filtered off the product then washed with cold water and the compounds were confirmed by their spectral data.

N′-Benzylidine-2-(trifluoromethyl)benzohydrazide (4a): This compound was obtained as a white solid. Yield (96 %); m.p.: 138-140 °C; R_f = 0.6 (hexane-EtOAc 6:4); LC-MS: *m/z* 293 (M+H), 315 (M+Na), 607 (2M+Na), (M, M+2). Calculated mass for the formula $C_{15}H_{11}N_2OF_3$ (m.w. 292).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.99 (s, 1H, NH), 8.28 (s, 1H, H_9), 7.86 (t, *J* = 7.6 Hz, 1H, H_4), 7.81 (d, *J* = 8.8 Hz, 1H, H_6), 7.75-7.69 (m, 3H, H_3, H_5, H_{13}), 7.47 (m, 2H, H_{11}, H_{15}), 7.33 (m, 2H, H_{12}, H_{14}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0 (C_7), 148.0 (C_9), 134.5 (d, C_1), 133.9 (C_{10}), 132.5 (C_4), 130.3 (C_3), 129.8 (C_{13}), 129.4 (C_6), 128.9 (C_5), 128.8 (C_{11} & C_{15}), 127.1 (C_{12} & C_{14}), 126.4 (m, C_2), 125.3 (m, C_8) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.99 (s, 1H, OH), 8.05 (s, 1H, H_9), 7.79 (m, 1H, H_4), 7.74-7.67 (m, 4H, H_3, H_5, H_6, H_{13}), 7.53 (d, *J* = 7.2 Hz, 2H, H_{11}, H_{15}), 7.33 (m, 2H, H_{12}, H_{14}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4 (C_7), 143.8 (C_9), 134.8 (d, C_1), 133.8 (C_{10}), 132.1 (C_4), 130.2 (C_3), 129.8 (C_{13}), 129.4 (C_6), 128.6 (C_{11} & C_{15}), 128.2 (C_5), 126.4 (C_{12} & C_{14}), 125.9 (m, C_2), 125.0 (m, C_8) ppm.

N′-(4-Hydroxybenzylidine)-2-(trifluoromethyl)benzohydrazide (4b): This compound was obtained as a white solid. Yield (91 %); m.p.: 240-242 °C; R_f = 0.55 (hexane-EtOAc 6:4); LC-MS: *m/z* 307 (M-H). Calculated mass for the formula $C_{15}H_{11}N_2O_2F_3$ (m.w. 308).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H, NH), 9.96 (s, 1H, OH), 8.17 (s, 1H, H_9), 7.86 (d, *J* = 8.0 Hz, 1H, H_6), 7.80 (t, *J* = 7.6 Hz, 1H, H_4), 7.68 (d, *J* = 7.6 Hz, 1H, H_3),7.65 (t, *J* = 7.2 Hz, 1H, H_5), 7.56 (d, *J* = 8.0 Hz, 2H, H_{11} & H_{15}), 6.85 (d, *J* = 8.8 Hz, 2H, H_{12} & H_{14}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7 (C_7), 159.5 (C_{13}), 148.2 (C_9), 134.7 (d, C_1), 132.5 (C_4), 132.0 (C_6), 130.2 (C_5), 128.9 (C_{11} & C_{15}), 128.8 (C_{10}), 128.2 (C_3), 126.3 (m, C_2), 125.2 (m, C_8), 115.7 (C_{12} & C_{14}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1H, OH), 9.81 (s, 1H, OH at C_{16}),7.93 (s, 1H, H_9), 7.74 (d, *J* = 8.0 Hz, 1H, H_6), 7.68 (m, 2H, H_4 & H_5), 7.50 (d, *J* = 7.6 Hz, 1H, H_3), 7.16 (d, *J* = 8.4 Hz, 2H, H_{11} & H_{15}), 6.70 (d, *J* = 8.4 Hz, 2H, H_{12} & H_{14}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.0 (C_7), 159.2 (C_{13}), 144.2 (C_9), 135.1 (d, C_1), 132.0 (C_4), 130.2 (C_6), 128.9 (C_5), 128.3 (C_3), 128.2 (C_{11} & C_{15}), 126.4 (C_{10}), 125.9 (m, C_2), 125.0 (m, C_8), 115.6 (C_{12} & C_{14}) ppm.

N′-(4-Nitrobenzylidine)-2-(trifluoromethyl)benzohydrazide (4c): This compound was obtained as a white solid. Yield (96 %); m.p.: 176-178 °C; R_f = 0.52 (hexane-EtOAc 6:4); LC- MS: *m/z* 336 (M-H). Calculated mass for the formula $C_{15}H_{10}N_3O_3F_3$ (m.w. 337).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.3 (s, 1H, NH), 8.39 (s, 1H, H_9), 8.31 (d, *J* = 8.8 Hz, 2H, H_{12} & H_{14}), 8.01 (d, *J* = 8.4 Hz, 2H, H_{11} & H_{15}), 7.88 (d, *J* = 7.6 Hz, 1H, H_6), 7.84 (t, *J* = 7.6 Hz, 1H, H_4), 7.78-7.72 (m, 2H, H_3 & H_5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4 (C_7), 148.0 (C_9), 145.6 (C_{13}), 140.2 (C_{10}), 134.2 (d, C_1), 132.6 (C_4), 130.5 (C_5), 129.7 (C_6), 128.9 (C_5), 128.2 (C_{11} & C_{15}), 126.5 (m, C_2), 125.4 (m, C_8), 124.0 (C_{12} & C_{14}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.3 (s, 1H, OH), 8.19 (d, *J* = 9.2 Hz, 2H, H_{12} & H_{14}), 8.16 (s, 1H, H_9), 7.85 (d, *J* = 7.6 Hz, 1H, H_6), 7.75-7.7 (m, 2H, H_3 & H_4), 7.58-7.56 (m, 3H, H_5, H_{11} & H_{15}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3 (C_7), 147.7 (C_9), 141.8 (C_{13}), 140.0 (C_{10}), 134.4 (d, C_1), 132.2 (C_4), 130.6 (C_3), 128.9 (C_6), 128.3 (C_5), 127.4 (C_{11} & C_{15}), 126.0 (m, C_2), 125.1 (m, C_8), 124.0 (C_{12} & C_{14}) ppm.

N′-(4-Chlorobenzylidine)-2-(trifluoromethyl)benzohydrazide (4d): This compound was obtained as a white solid. Yield (97 %); m.p.: 148-150 °C); R_f = 0.62 (hexane-EtOAc 6:4); LC-MS: *m/z* 325 (M-H). Calculated mass for the formula $C_{15}H_{10}N_2OClF_3$ (m.w. 326).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H, NH), 8.27(s, 1H, H_9), 7.87 (d, *J* = 7.6 Hz, 1H, H_6), 7.82 (t, *J* = 7.6 Hz, 1H, H_{14}), 7.76 (d, *J* = 8.0 Hz, 2H, H_{11} & H_{15}), 7.75 (m, 1H, H_5), 7.71 (d, *J* = 7.6 Hz, 1H, H_3), 7.54 (d, *J* = 8.0 Hz, 2H, H_{12} & H_{14}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1 (C_7), 146.7 (C_9), 134.7 (d, C_1), 132.9 (C_{10}), 132.6 (C_4), 132.2 (C_{13}), 130.3 (C_6), 129.8 (C_5), 128.9 (C_{12} & C_{14}), 128.8 (C_{11} & C_{15}), 128.1 (C_3), 126.4 (m, C_2), 125.2 (m, C_8) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H, OH), 8.04 (s, 1H, H_9), 7.84-7.69 (m, 4H, H_3, H_4, H_5 & H_6), 7.40 (d, *J* = 8.0 Hz, 2H, H_{11} & H_{15}), 7.34 (d, *J* = 8.0 Hz, 2H, H_{12} & H_{14}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4 (C_7), 142.7 (C_9), 134.3 (d, C_1), 132.7 (C_{10}), 132.1 (C_4), 130.3 (C_{13}), 129.5 (C_6), 128.8 (C_5), 128.3 (C_{12}& C_{14}), 128.1 (C_{11}& C_{15}), 128.1 (C_3), 125.9 (m, C_2), 125.0 (m, C_8) ppm.

N′-(4-Hydroxy-3-methoxybenzylidine)-2-(trifluoromethyl)benzohydrazide (4e): This compound was obtained as a white solid. Yield (92 %); m.p.: 196-198 °C; R_f = 0.56 (hexane-EtOAc 6:4); LC-MS: *m/z* 339 (M+H), 361 (M+ Na) and 533 (2M+Na). Calculated mass for the formula $C_{16}H_{13}N_2O_3F_3$ (m.w. 338).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.78 (s, 1H, NH), 9.6 (s, 1H, OH), 8.15 (s, 1H, H_9), 7.87-7.67 (m, 4H, H_3, H_4, H_5 & H_6), 7.32 (s, 1H, H_{11}), 7.08 (d, *J* = 7.6 Hz, 1H, H_{14}), 6.82 (d, *J* = 7.6 Hz, 1H, H_{15}), 3.85 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7 (C_7), 149.2 (C_9), 148.5 (C_{13}), 148.0 (C_{12}), 134.7 (d, C_1), 132.6 (C_4), 131.9 (C_3), 130.2 (C_6), 128.9 (C_5), 128.3 (C_{10}), 126.3 (m, C_2), 125.4 (m, C_8), 122.2 (C_{15}), 115.4 (C_{11}), 109.0 (C_{14}), 55.5 (OCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (s, 1H, OH), 9.6 (s, 1H, OH), 7.90 (s, 1H, H_9), 7.85-7.69 (m, 3H, H_3, H_4 & H_5), 7.52 (d, *J* = 7.2 Hz, 1H, H_6), 6.85-6.70 (m, 3H, H_{11}, H_{14} & H_{15}), 3.61 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2 (C_7), 148.6 (C_{13}), 147.6 (C_{12}), 143.8 (C_9), 134.9 (d, C_1), 131.9 (C_4), 130.2 (C_3), 129.2 (C_6), 128.9 (C_{10}), 128.4 (C_5), 125.8 (m, C_2), 125.0 (m, C_8), 120.6 (C_{15}), 115.4 (C_{11}), 109.6 (C_{14}), 55.2 (OCH_3) ppm.

N′-(3,4-Dimethoxybenzylidine)-2-(trifluoromethyl)-benzohydrazide (4f): This compound was obtained as a white solid. Yield (95 %); m.p.: 172-174 °C; R_f = 0.57 (hexane-EtOAc 6:4); LC-MS: *m/z* 353 (M+H). Calculated mass for the formula $C_{17}H_{15}N_2O_3F_3$ (m.w. 352).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H, NH), 8.88 (s, 1H, H_9), 7.87-7.68 (m, 4H, H_3, H_4, H_5 & H_6), 7.36 (s, 1H, H_{11}), 7.20 (d, *J* = 8.0 Hz, 1H, H_{15}), 7.04 (d, *J* = 8.0 Hz, 1H, H_{14}), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (C_7), 150.9 (C_{12}), 149.1 (C_{13}), 148.2 (C_9), 134.7 (d, C_1), 132.6 (C_4), 132.0 (C_3), 130.2 (C_6), 128.9 (C_5), 126.6 (C_{10}), 126.4 (m, C_2), 125.3 (m, C_8), 122.0 (C_{15}), 111.4 (C_{11}), 108.3 (C_{14}), 55.5 (OCH_3), 55.4 (OCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H, OH), 7.94 (s, 1H, H_9), 7.85-7.70 (m, 3H, H_3, H_4 & H_5), 7.53 (d, J = 7.2 Hz, 1H, H_6), 6.92-6.86 (m, 3H, H_{11}, H_{14} & H_{15}), 3.73 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3 (C_7), 150.4 (C_{13}), 148.7 (C_{12}), 143.3 (C_9), 135.0 (d, C_1), 132.0 (C_4), 130.3 (C_3), 129.2 (C_6), 128.3 (C_5), 126.7 (C_{10}), 125.7 (m, C_2), 125.0 (m, C_8), 120.5 (C_{15}), 111.5 (C_{11}), 108.6 (C_{14}), 55.5 (OCH_3), 55.0 (OCH_3) ppm.

N′-(4-Cyano-2-methoxybenzylidine-2-(trifluoromethyl)benzohydrazide (4g): This compound was obtained as a white solid. Yield (96 %); m.p.: 158-160 °C; R_f = 0.54 (hexane-EtOAc 6:4); LC-MS: *m/z* 346 (M-H). Calculated mass for the formula $C_{17}H_{12}N_3O_2F_3$ (m.w. 347).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (s, 1H, NH), 8.62 (s, 1H, H_9), 7.86-7.74 (m, 4H, H_3, H_4, H_5 & H_6), 7.63-7.50 (m, 2H, H_{12} & H_{14}), 7.27 (m, 1H, H_{15}), 3.92 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2 (C_7), 157.5 (C_{11}), 141.8 (C_9), 134.2 (d, C_1), 132.6 (C_4), 132.2 (C_3), 130.5 (C_6), 128.9 (C_5), 126.7 (C_{10}), 126.5 (m, C_2), 125.3 (C_{13}), 125.1 (m, C_8), 124.6 (C_{15}), 124.5 (CN), 118.5 (C_{14}), 115.5 (C_{12}), 56.4 (OCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (s, 1H, OH), 8.36 (s, 1H, H_9), 8.01 (s, 1H, H_{12}), 7.82-7.50 (m, 5H, H_3, H_4, H_5, H_{14} & H_{15}), 7.27 (m, 1H, H_6), 3.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.51 (C_7), 157.3 (C_{11}), 137.9 (C_9), 134.5 (d, C_1), 132.2 (C_4), 130.5 (C_3), 129.6 (C_6), 128.3 (C_5), 126.8 (C_{10}), 125.9 (m, C_2), 125.4 (m, C_8), 124.6 (CN), 118.5 (C_{15}), 115.6 (C_{13}), 113.2 (C_{14}), 112.8 (C_{12}), 56.4 (OCH_3) ppm.

N′-(2-Nitrobenzylidine)-2-(trifluoromethyl)benzohydrazide (4h): This compound was obtained as a white solid. Yield (96 %); m.p.: 159-161 °C; R_f = 0.53 (hexane-EtOAc 6:4); MS: *m/z* 336 (M-H). Calculated mass for the formula $C_{15}H_{10}N_3O_3F_3$ (m.w. 337).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H, NH), 8.57 (s, 1H, H_9), 8.29 (d, J = 7.6 Hz, 1H, H_{12}), 8.19-8.15 (m, 2H, H_{14} & H_{15}), 7.88 (d, J = 8.0 Hz, 1H, H_6), 7.82-7.74 (m, 4H, H_3, H_4, H_5 & H_{13}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.6 (C_7), 148.0 (C_{11}), 145.7 (C_9), 135.8 (C_{10}), 134.2 (d, C_1), 133.4 (C_{12}), 132.6 (C_4), 132.5 (C_3), 130.5 (C_6), 130.4 (C_{14}), 128.9 (C_5), 126.5 (m, C_2), 125.3 (m, C_8), 124.4 (C_{15}), 121.1 (C_{13}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H, OH), 8.41 (s, 1H, H_9), 8.18-8.15 (m, 2H, H_{12} & H_{14}), 7.84-7.22 (m, 4H, H_3, H_5, H_{13} & H_{15}), 7.62 (t, J = 8.0 Hz, 1H, H_4), 7.56 (d, J = 8.0 Hz, 1H, H_6) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4 (C_7), 148.2 (C_{11}), 141.6 (C_9), 135.7 (C_{10}), 134.5 (d, C_1), 133.4 (C_{12}), 132.5 (C_4), 132.2 (C_3), 130.3 (C_6), 129.6 (C_{14}), 128.3 (C_5), 126.0 (m, C_2), 125.1 (m, C_8), 124.0 (C_{15}), 120.7 (C_{13}) ppm.

N′-(4-(Dimethylamino)benzylidine-2-(trifluoromethyl)-benzohydrazide (4i): This compound was obtained as a white solid. Yield (94 %); m.p.: 149-151 °C; R_f = 0.57 (hexane-EtOAc 6:4); LC-MS: *m/z* 335 (M+H). Calculated mass for the formula $C_{17}H_{16}N_3OF_3$ (m.w. 335).

Keto form: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H, NH), 8.65 (s, 1H, H_9), 7.74-7.57 (m, 4H, H_3, H_4, H_5 & H_6), 7.27 (d, J = 7.6 Hz, 2H, H_{11} & H_{15}), 6.57 (d, J = 8.0 Hz, 2H, H_{12} & H_{14}), 2.95 (s, 6H, NCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.26 (C_7), 151.7 (C_{13}), 150.0 (C_9), 134.2 (d, C_1), 132.2 (C_4), 131.3 (C_3), 130.28 (C_6), 129.2 (C_5), 128.7 (C_{11} & C_{15}), 128.6 (C_{10}), 126.2 (m, C_2), 125.1 (m, C_8), 111.6 (C_{12} & C_{14}), 40.1 ($N(CH_3)_2$) ppm.

Enol form: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H, OH), 8.02(s, 1H, H_9), 7.72-7.50 (m, 6H, H_3, H_4, H_5, H_6, H_{11} & H_{15}), 6.68 (d, J = 8.0 Hz, 2H, H_{12} & H_{14}), 3.02 (s, 6H, NCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (C_7), 152.1 (C_{13}), 145.5 (C_9), 134.1 (d, C_1), 132.1 (C_4), 131.3 (C_3), 129.5 (C_{11} & C_{15}), 129.3 (C_6), 129.2 (C_5), 128.7 (C_{10}), 126.4 (m, C_2), 121.2 (m, C_8), 111.6 (C_{12} & C_{14}), 40.1 ($N(CH_3)_2$) ppm.

N′-(3,4,5-Trimethoxybenzylidine)-2-(trifluoromethyl)-benzohydrazide (4j): This compound was obtained as a white solid. Yield (95 %); m.p.163-165 °C; R_f = 0.53 (hexane-EtOAc 6:4); LC-MS: *m/z* 383 (M+H). Calculated mass for the formula $C_{18}H_{17}N_2O_4F_3$ (m.w. 382).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.95 (s, 1H, NH), 8.21 (s, 1H, H_9), 7.87 (d, J = 8.0 Hz, 1H, H_6), 7.81 (t, J = 7.6 Hz, 1H, H_4), 7.74 (d, J = 8.0 Hz, 1H, H_3), 7.69 (t, J = 7.6 Hz, 1H, H_5), 7.05 (s, 2H, H_{11} & H_{15}), 3.85 (s, 6H, OCH_3), 3.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0 (C_7), 153.2 (C_{12} & C_{14}), 147.9 (C_9), 139.4 (C_{13}), 134.5 (d, C_1), 132.6 (C_4), 131.9 (C_3), 130.0 (C_6), 129.4 (C_5), 128.9 (C_{10}), 126.4 (m, C_2), 125.0 (m, C_8), 104.4 (C_{11} & C_{15}), 55.9 (OCH_3, C_{12} & C_{14}), 55.6 (OCH_3, C_{13}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.05 (s, 1H, OH), 7.93 (s, 1H, H_9), 7.79 (m, 1H, H_5), 7.72 (m, 1H, H_3), 7.67 (m, 1H, H_4), 7.53 (d, J = 7.6 Hz, 1H, H_6), 6.66 (s, 2H, H_{11} & H_{15}), 3.72 (s, 6H, OCH_3), 3.61 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5 (C_7), 152.9 (C_{12} & C_{14}), 142.8 (C_9), 138.9 (C_{13}), 134.9 (d, C_1), 132.6 (C_4), 131.8 (C_3), 129.5 (C_6), 129.2 (C_5), 128.3 (C_{10}), 125.7 (m, C_2), 125.2 (m, C_8), 103.8 (C_{11} & C_{15}), 60.1 (OCH_3, C_{12} & C_{14}), 60.0 (OCH_3, C_{13}) ppm.

N′-(2,4,6-Trimethoxybenzylidine)-2-(trifluoromethyl)-benzohydrazide (4k): This compound was obtained as a white solid. Yield (96 %); m.p.: 144-146 °C; R_f = 0.54 (hexane-EtOAc 6:4); LC-MS: *m/z* 383 (M+H). Calculated mass for the formula $C_{17}H_{18}N_2O_4F_3$ (m.w. 382).

Keto form: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (s, 1H, NH), 8.09 (s, 1H, H_9), 7.71-7.67 (m, 2H, H_4 & H_6), 7.59-7.51 (m, 2H, H_3 & H_5), 6.14 (s, 2H, H_{12} & H_{14}), 3.87 (s, 3H, OCH_3), 3.60 (s, 6H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C_7), 162.7 (C_{13}), 160.5 (C_{11} & C_{15}), 139.8 (C_9), 131.7 (d, C_1), 131.02 (C_4), 129.5 (C_3), 128.9 (C_6), 128.8 (C_5), 126.3 (m, C_2), 125.3 (m, C_8), 104.2 (C_{10}), 91.0 (C_{12} & C_{14}), 55.7 (OCH_3), 55.3 (OCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H, OH), 7.71-79 (m, 1H, H_6), 7.67 (s, 1H, H_9), 7.62-7.49 (m, 3H, H_3, H_4 & H_5), 6.02 (s, 2H, H_{12} & H_{14}), 3.93 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (C_7), 161.3 (C_{13}), 160.5 (C_{11} & C_{15}), 139.9 (C_9), 131.8 (d, C_1),

131.0 (C_4), 129.5 (C_3), 128.9 (C_6), 128.8 (C_5), 125.9 (m, C_2), 125.0 (m, C_8), 104.1 (C_{10}), 90.7 (C_{12} & C_{14}), 56.3 (OCH_3), 55.6 (OCH_3) ppm.

N′-(4,5-Dimethoxy-2-nitrobenzylidine)-2-(trifluoromethyl)benzohydrazide (4l): This compound was obtained as a white solid. Yield (94 %); m.p.:158-160 °C; R_f = 0.52 (hexane-EtOAc 6:4); LC-MS: *m/z* 398 (M+H). Calculated mass for the formula $C_{17}H_{14}N_3O_5F_3$ (m.w. 397).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H, NH), 8.79 (s, 1H, H_9), 7.88-7.71 (m, 3H, H_3, H_4, H_5 & H_6), 7.66 (s, 1H, H_{12}), 7.56 (s, 1H, H_{15}), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7 (C_7), 152.7 (C_{11}), 149.8 (C_9), 143.9 (C_{14}), 140.8 (C_{13}), 134.2 (d, C_1), 132.6 (C_4), 132.1 (C_3), 130.4 (C_6), 128.9 (C_5), 128.3 (C_{10}), 126.4 (m, C_2), 125.3 (m, C_8), 122.9 (C_{12}), 107.7 (C_{15}), 56.3 (OCH_3), 56.2 (OCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H, NH), 8.54 (s, 1H, H_9), 7.84-7.69 (m, 4H, H_3, H_4, H_5 & H_6), 7.59 (s, 1H, H_{12}), 6.86 (s, 1H, H_{15}), 3.85 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1 (C_7), 152.4 (C_{11}), 149.3 (C_9), 141.4 (C_{14}), 139.1 (C_{13}), 134.7 (d, C_1), 132.6 (C_4), 132.1 (C_3), 130.4 (C_6), 129.4 (C_5), 128.9 (C_{10}), 125.8 (m, C_2), 125.1 (m, C_8), 123.0 (C_{12}), 108.1 (C_{15}), 56.2 (OCH_3), 55.5 (OCH_3) ppm.

N′-[(1H-Indol-3-yl)methylene]-2-(trifluoromethyl)-benzohydrazide (4m): This compound was obtained as a white solid. Yield (96 %); m.p.: 230-232 °C; R_f = 0.45 (hexane-EtOAc 6:4); LC-MS: *m/z* 330 (M-H). Calculated mass for the formula $C_{17}H_{12}N_3OF_3$ (m.w. 331).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H, NH), 11.57 (s, 1H, NH), 8.45 (s, 1H, H_9), 8.30 (d, *J* = 7.6 Hz, 1H, H_6), 7.87-7.69 (m, 4H, H_3, H_4, H_5 & H_{10}), 7.56 (d, *J* = 7.2 Hz, 1H, H_{12}), 7.32 (d, *J* = 8.0 Hz, 1H, H_{15}), 7.23 (t, *J* = 8.0 Hz, 1H, H_{14}), 7.05 (t, *J* = 8.0 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.8 (C_7), 145.1 (C_9), 136.8 (C_{16}), 135.9 (d, C_1), 132.5 (C_4), 130.6 (C_3), 129.9 (C_6), 129.0 (C_5), 128.1 (C_{10}), 126.3 (m, C_2), 125.1 (m, C_8), 124.3 (C_{17}), 122.6 (C_{13}), 121.3 (C_{15}), 119.8 (C_{11}), 111.8 (C_{12}), 111.4 (C_{14}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.59 (s, 1H, NH), 11.40 (s, 1H, OH), 8.19 (s, 1H, H_9), 7.87-7.69 (m, 5H, H_3, H_4, H_5, H_6 & H_{10}), 7.46 (d, *J* = 8.0 Hz, 1H, H_{12}), 7.17 (t, *J* = 7.2 Hz, 1H, H_{14}), 6.96 (d, *J* = 7.6 Hz, 1H, H_{15}), 6.70 (t, *J* = 7.6 Hz, 1H, H_{13}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.4 (C_7), 140.5 (C_9), 137.0 (C_{16}), 135.2 (d, C_1), 132.1 (C_4), 130.0 (C_3), 129.0 (C_5), 128.8 (C_6), 128.1 (C_{10}), 125.9 (m, C_2), 125.2 (m, C_8), 123.8 (C_{17}), 122.3 (C_{13}), 121.9 (C_{15}), 120.4 (C_{11}), 111.5 (C_{12}), 111.3 (C_{14}) ppm.

N′-[(5-Bromo-1-methyl-1H-indol-3-yl)methylene]-2-(trifluoromethyl)benzohydrazide (4n): This compound was obtained as a white solid. Yield (92 %); m.p.: 180-182 °C; R_f = 0.46 (hexane-EtOAc 6:4); LC-MS: *m/z* 424 (M+H). Calculated mass for the formula $C_{18}H_{13}N_3OBrF_3$ (m.w. 423).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.75 (s, 1H, NH), 8.13 (s, 1H, H_9), 7.86 (d, *J* = 8.0 Hz, 1H, H_6), 7.80 (t, *J* = 7.2 Hz, 1H, H_4), 7.74 (s, 1H, H_{10}), 7.72 (t, *J* = 7.2 Hz, 1H, H_5), 7.57 (d, *J* = 7.6 Hz, 1H, H_3), 7.37 (d, *J* = 8.8 Hz, 1H, H_{15}), 7.24 (dd, *J* = 1.6, 8.4 Hz, 1H, H_{14}), 7.15 (d, *J* = 1.2 Hz, 1H, H_{12}), 3.74 (s, 3H, NCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9 (C_7), 139.5 (C_9), 136.1 (C_{16}), 135.5 (d, C_1), 134.8 (C_{13}), 132.6 (C_4), 132.2 (C_3), 129.4 (C_6), 129.0 (C_5), 127.9 (C_{10}), 126.4 (m, C_8), 126.0 (m, C_2), 125.7 (C_{11}), 124.9 (C_{17}), 123.6 (C_{14}), 113.2 (C_{12}), 112.0 (C_{15}), 32.8 (NCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H, OH), 7.88 (s, 1H, H_9), 7.85-7.70 (m, 5H, H_3, H_4, H_5, H_6 & H_{10}), 7.57 (d, *J* = 7.6 Hz, 1H, H_{15}), 7.42 (dd, *J* = 1.6, 8.2 Hz, 1H, H_{14}), 7.14 (d, *J* = 1.2 Hz, 1H, H_{12}), 3.83 (s, 3H, NCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.4 (C_7), 144.1 (C_9), 136.3 (C_{16}), 135.6 (d, C_1), 134.8 (C_{13}), 132.6 (C_4), 130.1 (C_3), 129.0 (C_6), 127.9 (C_5), 126.4 (m, C_8), 126.1 (m, C_2), 125.2 (C_{10}), 124.9 (C_{11}), 124.1 (C_{17}), 113.5 (C_{14}), 112.4 (C_{12}), 109.9 (C_{15}), 33.0 (NCH_3) ppm.

N′-[(1-Ethyl-1H-indol-3-yl)methylene]-2-(trifluoromethyl)benzohydrazide (4o): This compound was obtained as a white solid. Yield (94 %); m.p.: 155-157 °C; R_f = 0.48 (hexane-EtOAc 6:4); LC-MS: *m/z* 360 (M+H). Calculated mass for the formula $C_{18}H_{13}N_3OBrF_3$ (m.w. 359).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H, NH), 8.48 (s, 1H, H_9), 8.02 (s, 1H, H_{10}), 7.80 (d, *J* = 8.0 Hz, 1H, H_6), 7.70-7.58 (m, 3H, H_3, H_4 & H_5), 7.28 (d, *J* = 8.0 Hz, 1H, H_{15}), 7.24 (d, *J* = 7.6 Hz, 1H, H_{12}), 7.18 (t, *J* = 7.6 Hz, 1H, H_{14}), 6.89 (t, *J* = 7.6 Hz, 1H, H_{13}), 4.12 (q, *J* = 7.2 Hz, 2H, NCH_2), 1.44 (t, *J* = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2 (C_7), 140.4 (C_9), 136.8 (C_{16}), 134.6 (d, C_1), 132.2 (C_4), 131.4 (C_3), 130.7 (C_6), 129.1 (C_{10}), 128.5 (C_5), 126.3 (m, C_2), 125.7 (m, C_8), 125.1 (C_{15}), 123.0 (C_{17}), 122.4 (C_{12}), 120.8 (C_{11}), 111.1 (C_{14}), 109.4 (C_{13}), 41.3 (CH_2), 15.2 (CH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H, OH), 8.4 (s, 1H, H_9), 7.75 (d, *J* = 8.0 Hz, 1H, H_6), 7.70-7.58 (m, 3H, H_3, H_4 & H_5), 7.53 (s, 1H, H_{10}), 7.37-7.22 (m, 4H, H_{12}, H_{13}, H_{14} & H_{15}), 4.19 (q, *J* = 7.6 Hz, 2H, NCH_2), 1.50 (t, *J* = 7.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (C_7), 138.3 (C_9), 136.8 (C_{16}), 134.8 (d, C_1), 132.1 (C_4), 131.4 (C_3), 130.2 (C_6), 129.3 (C_{10}), 128.4 (C_5), 126.2 (m, C_2), 125.5 (m, C_8), 125.0 (C_{15}), 123.1 (C_{17}), 122.2 (C_{12}), 121.5 (C_{11}), 110.8 (C_{14}), 109.6 (C_{13}), 41.4 (CH_2), 15.2 (CH_3) ppm.

N′-[(5-Bromo-1-ethyl-1H-indol-3-yl)methylene]-2-(trifluoromethyl)benzohydrazide (4p): This compound was obtained as a white solid. Yield (92 %); m.p.: 160-162 °C; R_f = 0.48 (hexane-EtOAc 6:4); LC-MS: *m/z* 437 (M-H). Calculated mass for the formula $C_{19}H_{15}N_3OBrF_3$ (m.w. 438).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H, NH), 8.45 (s, 1H, H_9), 8.14 (s, 1H, H_{10}), 7.87-7.71 (m, 4H, H_3, H_6, H_{12} & H_{14}), 7.56 (t, *J* = 7.6 Hz, 1H, H_4), 7.42 (t, *J* = 7.6 Hz, 1H, H_5), 7.22 (d, *J* = 8.8 Hz, 1H, H_{15}), 4.16 (q, *J* = 6.0 Hz, 2H, CH_2), 1.32 (t, *J* = 6.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4 (C_7), 139.6 (C_9), 135.5 (C_{16}), 135.1 (C_{13}), 133.3 (d, C_1), 132.2 (C_4), 129.4 (C_3), 127.9 (C_5), 126.5 (C_6), 126.1 (m, C_2), 125.9 (C_{10}), 125.3 (m, C_8), 124.9 (C_{11}), 123.8 (C_{17}), 113.2 (C_{12}), 112.0 (C_{15}), 110.2 (C_{14}), 40.7 (CH_2), 15.1 (CH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H, OH), 8.40 (s, 1H, H_9), 7.96 (s, 1H, H_{10}), 7.85-7.72 (m, 4H, H_3, H_6, H_{12} & H_{14}), 7.56 (t, *J* = 7.6 Hz, 1H, H_4), 7.42 (t, *J* = 7.6 Hz, 1H, H_5), 7.22 (d, *J* = 8.8 Hz, 1H, H_{15}), 4.24 (q, *J* = 6.4 Hz, 2H, CH_2), 1.40 (t, *J* = 6.8 Hz, 3H, CH_3) ppm; ^{13}C

NMR (100 MHz, DMSO-d_6): δ 162.4 (C_7), 144.1 (C_9), 135.5 (C_{16}), 135.1 (C_{13}), 134.0 (d, C_1), 132.5 (C_4), 130.1 (C_3), 129.0 (C_5), 126.5 (C_6), 126.0 (m, C_2), 125.3 (C_{10}), 125.1 (m, C_8), 124.3 (C_{11}), 122.2 (C_{17}), 113.5 (C_{12}), 112.5 (C_{15}), 110.2 (C_{14}), 40.9 (CH_2), 15.1 (CH_3) ppm.

N′-[(1-Benzyl-1H-indol-3-yl)methylene]-2-(trifluoromethyl)benzohydrazide (4q): This compound was obtained as a white solid. Yield (95 %); m.p.: 208-210 °C; R_f = 0.49 (hexane-EtOAc 6:4); LC-MS: *m/z* 422 (M+1). Calculated mass for the formula $C_{24}H_{18}N_3OF_3$ (m.w. 421).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.64 (s, 1H, NH), 8.45 (s, 1H, H_9), 8.31 (d, *J* = 6.0 Hz, 1H, H_6), 8.19 (s, 1H, H_{10}), 7.88-7.72 (m, 3H, H_3, H_4, & H_5), 7.55 (t, *J* = 6.8 Hz, 1H, H_{14}), 7.40 (d, *J* = 7.6 Hz, 1H, H_{12}), 7.33-7.21 (m, 6H, phenyl, H_{15}), 7.06 (t, *J* = 8.4 Hz, 1H, H_{13}), 5.47 (s, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.41 (C_7), 144.4 (C_9), 137.4 (C_{10}), 136.9 (C_{16}), 135.7 (d, C_1), 133.6 (C_4), 132.3 (C_3), 130.0 (C_6), 128.8 (C_5), 128.5 (phenyl 2C), 128.1 (C_{11}), 127.5 (phenyl 1C), 127.12 (phenyl 2C), 126.2 (m, C_2), 125.1 (m, C_8), 124.5 (C_{17}), 122.8 (C_{15}), 121.6 (C_{13}), 120.8 (C_{12}), 111.0 (phenyl 1C), 110.6 (C_{14}), 49.2 (CH_2) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H, OH), 8.02 (s, 1H, H_9), 7.88-7.72 (m, 5H, H_3, H_4, H_5, H_6 & H_{10}), 7.55 (t, *J* = 6.8 Hz, 1H, H_{14}), 7.33-7.20 (m, 6H, phenyl, H_{15}), 6.97 (d, *J* = 7.2 Hz, 1H, H_{12}), 6.74 (t, *J* = 6.4 Hz, 1H, H_{13}), 5.39 (s, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9 (C_7), 140.0 (C_9), 137.4 (C_{10}), 136.8 (C_{16}), 135.2 (d, C_1), 133.1 (C_4), 132.6 (C_3), 130.0 (C_6), 129.0 (C_5), 128.6 (phenyl 2C), 128.1 (C_{11}), 127.5 (phenyl 1C), 127.0 (phenyl 2C), 125.9 (m, C_2), 125.1 (m, C_8), 124.9 (C_{17}), 122.6 (C_{15}), 122.1 (C_{13}), 120.2 (C_{12}), 111.0 (phenyl 1C), 110.4 (C_{14}), 49.3 (CH_2) ppm.

N′-[(1-Benzyl-5-bromo-1H-indol-3-yl)methylene]-2-(trifluoromethyl)benzohydrazide (4r): This compound was obtained as a white solid. Yield (91 %); m.p.: 173-175 °C; R_f = 0.5 (hexane-EtOAc 6:4); LC-MS: *m/z* 501 (M+H). Calculated mass for the formula $C_{24}H_{17}N_3OBrF_3$ (m.w. 500).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H, NH), 8.45 (s, 1H, H_9), 8.07 (s, 1H, H_{10}), 7.86 (d, *J* = 7.6 Hz, 1H, H_6), 7.80 (t, *J* = 7.6 Hz, 1H, H_4), 7.73 (d, *J* = 7.6 Hz, 1H, H_3), 7.71 (t, *J* = 7.2 Hz, 1H, H_5), 7.55 (d, *J* = 2.0 Hz, 1H, H_{12}), 7.33 (d, *J* = 7.6 Hz, 1H, H_{14}), 7.29 (d, *J* = 7.2 Hz, 2H, phenyl), 7.23 (d, *J* = 7.6 Hz, 1H, H_{15}), 7.20-7.15 (m, 3H, phenyl), 5.48 (s, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1 (C_7), 144.2 (C_9), 137.1 (C_{10}), 135.6 (C_{16}), 135.4 (C_{13}), 134.3 (d, C_1), 132.5 (C_4), 130.1 (C_3), 129.5 (C_6), 129.0 (C_5), 128.6 (phenyl 2C), 127.6 (C_{11}), 127.5 (phenyl 1C), 126.9 (phenyl 2C), 126.4 (C_{14}), 126.0 (m, C_2), 124.3 (m, C_8), 123.8 (C_{17}), 113.4 (C_{15}), 112.5 (C_{12}), 110.6 (phenyl 1C), 49.5 (CH_2) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H, OH), 8.16 (s, 1H, H_9), 7.94 (s, 1H, H_{10}), 7.85 (d, *J* = 7.6 Hz, 1H, H_6), 7.80 (t, *J* = 7.6 Hz, 1H, H_4), 7.74 (d, *J* = 7.6 Hz, 1H, H_3), 7.71 (t, *J* = 7.2 Hz, 1H, H_5), 7.53 (d, *J* = 2.0, 1H, H_{12}), 7.38 (d, *J* = 8.8 Hz, 1H, H_{14}), 7.25 (d, *J* = 7.2 Hz, 2H, phenyl), 7.20-7.15 (m, 4H, phenyl, H_{15}), 5.39 (s, 2H, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9 (C_7), 139.5 (C_9), 137.1 (C_{10}), 135.5 (C_{16}), 135.4 (C_{13}), 134.9 (d, C_1), 132.5 (C_4), 130.1 (C_3), 129.5 (C_6), 128.6 (phenyl 2C), 127.9 (C_{11}), 127.5 (phenyl 1C), 127.1 (C_5), 126.9 (phenyl 2C), 126.4 (C_{14}), 125.1 (m, C_2), 124.3 (m, C_8), 123.8 (C_{17}), 113.6 (C_{15}), 112.5 (C_{12}), 110.5 (phenyl 1C), 49.3 (CH_2) ppm.

N′-[(1,3-Diphenyl-1H-pyrazol-4-yl)methylene]-2-(trifluoromethyl)benzohydrazide (4s): This compound was obtained as a white solid. Yield (97 %); m.p.:106-108 °C; R_f= 0.36 (hexane-EtOAc 6:4); LC-MS: *m/z* 433 (M-H). Calculated mass for the formula $C_{24}H_{17}N_4OF_3$ (m.w. 434).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.9 (s, 1H, NH), 9.0 (s, 1H, H_{12}), 8.42 (s, 1H, H_9), 8.05 (d, *J* = 8.0 Hz, 1H, H_6), 7.86 (d, *J* = 7.6 Hz, 1H, H_3), 7.74-7.69 (m, 3H, H_{20}, H_{22} & H_{24}), 7.57-7.46 (m, 7H, H_{21}, H_{23}, H_{13}, H_{14}, H_{15}, H_{16} and H_{17}, 7.39 (t, *J* = 7.6 Hz, 1H, H_4), 7.28 (t, *J* = 8.0 Hz, 1H, H_5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.5 (C_7), 151.9 (C_9), 141.3 (C_{10}), 139.0 (C_{18}), 137.9 (C_{12}), 134.5 (d, C_1), 132.6 (C_4), 131.8 (C_3), 130.3 (C_6), 129.6 (C_{20} & C_{24}), 128.9 (C_5), 128.7 (C_{21} & C_{23}), 128.3 (C_{14} & C_{15}), 128.2 (C_{11}), 127.2 (C_{19}), 127.1 (C_{22}), 126.4 (m, C_2), 125.0 (m, C_8), 118.8 (C_{13} & C_{17}), 116.5 (C_{15}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.80 (s, 1H, OH), 8.55 (s, 1H, H_{12}), 8.22 (s, 1H, H_9), 7.82 (d, *J* = 7.2 Hz, 1H, H_6), 7.79 (d, *J* = 7.2 Hz, 1H, H_3), 7.74-7.69 (m, 3H, H_{20}, H_{22} & H_{24}), 7.62-7.46 (m, 7H, H_{21}, H_{23}, H_{13}, H_{14}, H_{15}, H_{16} and H_{17}), 7.35 (t, *J* = 7.2 Hz, 1H, H_4), 7.28 (t, *J* = 8.0 Hz, 1H, H_5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7 (C_7), 150.8 (C_9), 138.8 (C_{10}), 137.9 (C_{18}), 134.6 (C_{12}), 134.5 (d, C_1), 132.5 (C_4), 132.1 (C_3), 130.3 (C_6), 129.6 (C_{20} & C_{24}), 128.9 (C_5), 128.6 (C_{21} & C_{23}), 128.4 (C_{11}), 128.2 (C_{14} & C_{16}), 127.2 (C_{19}), 126.9 (C_{22}), 126.2 (m, C_2), 125.0 (m, C_8), 118.7 (C_{13} & C_{17}), 116.3 (C_{15}) ppm.

N′-[3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]methylene-2-(trifluoromethyl)benzohydrazide (4t): This compound was obtained as a white solid. Yield (95 %); m.p.: 176-178 °C; R_f = 0.36 (hexane-EtOAc 6:4); LC-MS: *m/z* 465 (M+H). Calculated mass for the formula $C_{25}H_{19}N_4O_2F_3$ (m.w. 464).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H, NH), 7.96 (s, 1H, H_{12}), 7.90 (s, 1H, H_9), 7.75 (d, *J* = 8.4 Hz, 2H, H_{20} & H_{24}), 7.60-7.41 (m, 8H, H_3, H_4, H_6, H_{13}, H_{14}, H_{15}, H_{16} & H_{17}), 7.31 (t, *J* = 7.2 Hz, 1H, H_5), 6.95 (d, *J* = 8.8 Hz, 2H, H_{21} & H_{23}), 3.81 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8 (C_7), 160.0 (C_{22}), 153.0 (C_9), 142.5 (C_{10}), 139.4 (C_{18}), 138.2 (C_{12}), 133.6 (d, C_1), 132.1 (C_4), 131.5 (C_3), 130.4 (C_6), 129.9 (C_{20} & C_{24}), 129.56 (C_{14} & C_{16}), 129.0 (C_5), 128.5 (C_{11}), 127.2 (C_{15}), 127.0 (C_{19}), 126.3 (m, C_2), 125.0 (m, C_8), 119.2 (C_{13} & C_{17}), 114.24 (C_{21} & C_{23}), 55.3 (OCH_3) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H, OH), 8.65 (s, 1H, H_{12}), 8.18 (s, 1H, H_9), 7.74 (d, *J* = 8.4 Hz, 2H, H_{20} & H_{24}), 7.65-7.41(m, 8H, H_3, H_4, H_6,H_{13}, H_{14}, H_{15}, H_{16} & H_{17}), 7.29 (t, *J* = 7.2 Hz, 1H, H_5), 6.89 (d, *J* = 8.8 Hz, 2H, H_{21} & H_{23}), 3.83 (s, 3H, OCH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9 (C_7), 159.9 (C_{22}), 152.5 (C_9), 142.5 (C_{10}), 139.4 (C_{18}), 138.3 (C_{12}), 133.5 (d, C_1), 132.1 (C_4), 131.5 (C_3), 130.4 (C_6), 129.8 (C_{20} & C_{24}), 129.4 (C_{14} & C_{16}), 129.0 (C_5), 128.5 (C_{11}), 127.1 (C_{19}), 126.7 (C_{15}), 126.2 (m, C_2), 124.8 (m, C_8), 119.4 (C_{13} & C_{17}), 114.1 (C_{21} & C_{23}), 55.3 (OCH_3) ppm.

N′-[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]methylene-2-(trifluoromethyl)benzohydrazide (4u): This compound was obtained as a white solid. Yield (96 %); m.p.:

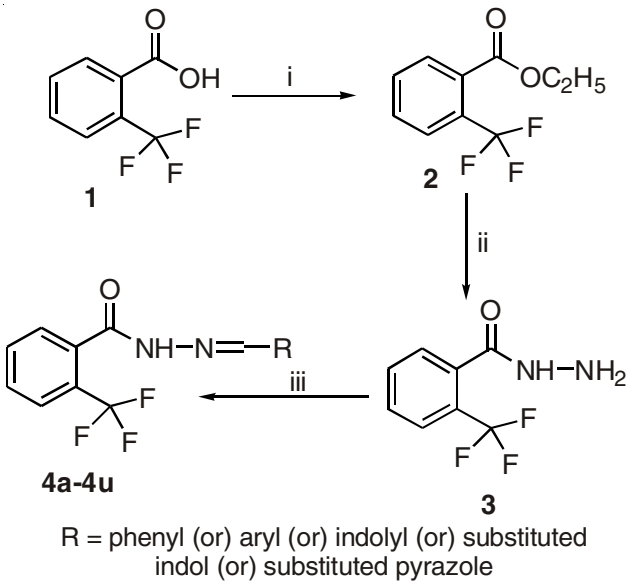
156-158 °C; R_f = 0.38 (hexane-EtOAc 6:4); LC-MS: *m/z* 467(M-H). Calculated mass for the formula $C_{24}H_{16}N_4OClF_3$ (m.w. 468).

Keto form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.51 (s, 1H, NH), 8.68 (s, 1H, H_{12}), 7.99 (s, 1H, H_9), 7.78 (d, *J* = 8.0 Hz, 2H, H_{20} & H_{24}), 7.66-7.32 (m, 11H, H_3, H_4, H_5, H_6, H_{13}, H_{14}, H_{15}, H_{16}, H_{17}, H_{21} & H_{23}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2 (C_7), 151.3 (C_9),141.9 (C_{10}), 139.3 (C_{18}), 137.3 (C_{12}), 134.8 (C_{22}), 134.5 (d, C_1), 132.2 (C_4), 131.5 (C_3), 130.6 (C_6), 129.8 (C_{20} & C_{24}), 129.6 (C_{14} & C_{16}), 129.5 (C_5), 129.1 (C_{11}), 129.0 (C_{21} & C_{23}), 128.6 (C_{15}), 128.4 (C_{19}), 127.4 (m, C_2), 126.5 (m, C_8), 119.4 (C_{13} & C_{17}) ppm.

Enol form: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (s, 1H, OH), 8.21 (s, 1H, H_{12}), 7.89 (s, 1H, H_9), 7.74 (d, *J* = 7.2 Hz, 2H, H_{20} & H_{24}), 7.66-7.32 (m, 11H, H_3, H_4, H_5, H_6, H_{13}, H_{14}, H_{15}, H_{16}, H_{17}, H_{21} & H_{23}) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9 (C_7), 151.9 (C_9), 141.9 (C_{10}), 139.2 (C_{18}), 137.3 (C_{12}), 134.8 (C_{22}), 133.6 (d, C_1), 132.2 (C_4), 131.5 (C_3), 130.6 (C_6), 129.8 (C_{20} & C_{24}), 129.6 (C_5), 129.5 (C_{14} & C_{16}), 129.1 (C_{11}), 128.6 (C_{21}& C_{23}), 127.4 (C_{15}), 127.3 (C_{19}), 126.6 (m, C_2), 126.4 (m, C_8), 119.3 (C_{13} & C_{17}) ppm.

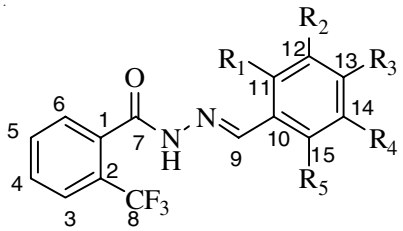
RESULTS AND DISCUSSION

In order to develop the new and biologically active trifluoromethyl benzohydrazide derivatives in this investigation we tried with 2-trifluoromethyl benzoic acid (**1**) in three consecutive steps (**Scheme-I**).



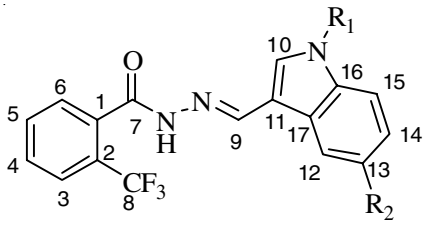
Scheme-I: Reagents & conditions: i) EtOH, H_2SO_4, reflux. ii) $NH_2NH_2.H_2O$, EtOH, reflux iii) RCHO, KOH, EtOH, room temparature

By using the above scheme (**Scheme-I**), here we synthesized and reported 2-(trifluoromethyl) benzohydrazide derivatives as three types namely phenyl (or) substituted phenyl N'-methylidene benzohydrazides (**4a-4l**; Fig. 1), N'-indol (or) substituted indol N'-methylydine benzohydrazides (**4m-4r**; Fig. 2) and substituted pyrazole N'-methylydine benzohydrazides (**4s-4u**; Fig. 3) derivatives. The details in respect of reaction conditions, aldehydes utilized and yields of the products were reported in Table-1.



4a: $R_1 = R_2 = R_3 = R_4 = R_5 = H$; **4b:** $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OH$; **4c:** $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = NO_2$; **4d:** $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Cl$; **4e:** $R_1 = R_2 = R_5 = H$, $R_3 = OH$, $R_4 = OCH_3$; **4f:** $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = OCH_3$; **4g:** $R_2 = R_4 = R_5 = H$, $R_1 = OCH_3$, $R_3 = CN$; **4h:** $R_1 = NO_2$, $R_2 = R_3 = R_4 = R_5 = H$; **4i:** $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = N(CH_3)_2$; **4j**: $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = OCH_3$; **4k**: $R_2 = R_4 = H$, $R_1 = R_3 = R_5 = OCH_3$; **4l**: $R_1 = R_4 = H$, $R_2 = R_3 = OCH_3$, $R_5 = NO_2$

Fig. 1. Phenyl hydrazides(**4a- 4l**)



4m: $R_1 = R_2 = H$; **4n:** $R_1 = CH_3$, $R_2 = Br$; **4o**: $R_1 = C_2H_5$, $R_2 = H$; **4p**: $R_1 = C_2H_5$, $R_2 = Br$; **4q**: R_1 = Benzyl, $R_2 = H$; **4r**: R_1 = Benzyl, $R_2 = Br$

Fig. 2. Indol hydrazides **(4m-4r)**

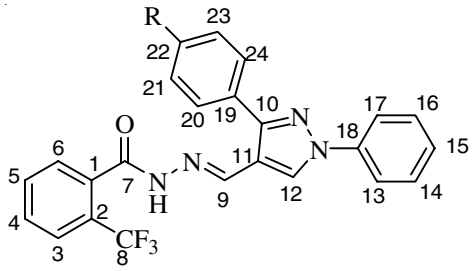
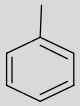
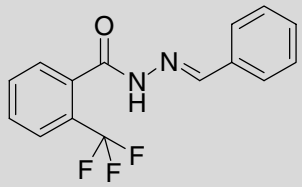
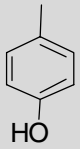
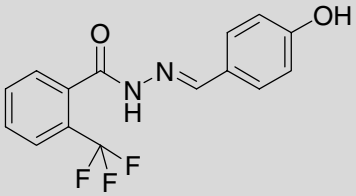
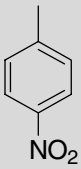
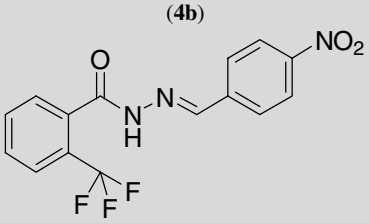
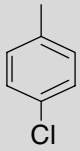
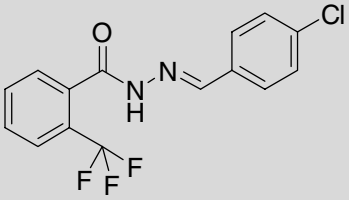
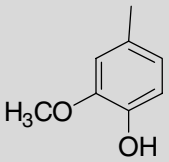
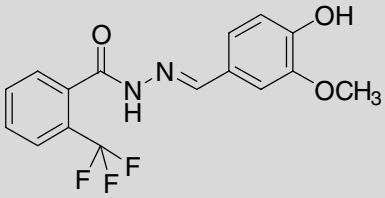
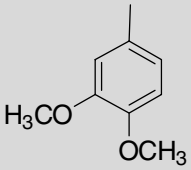
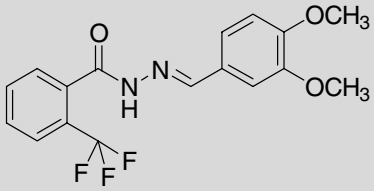
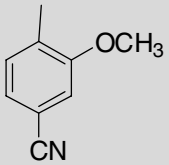
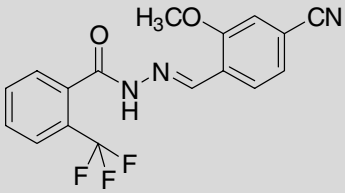
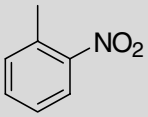
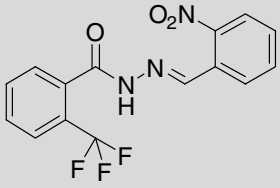


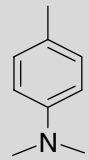
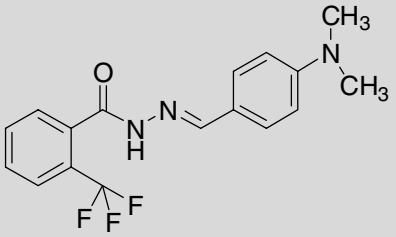
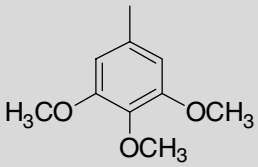
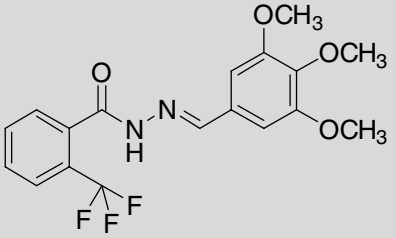
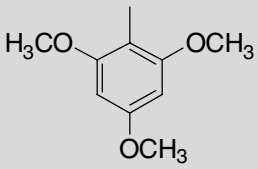
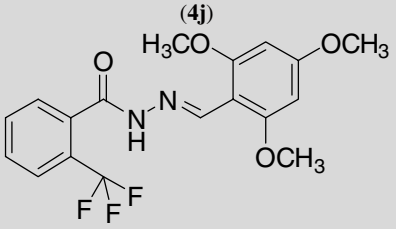
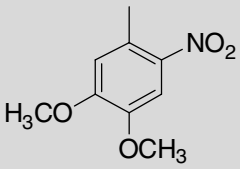
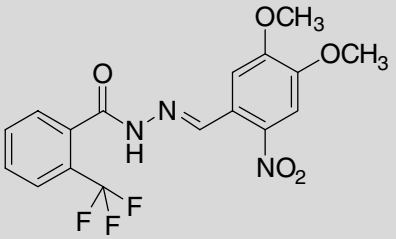
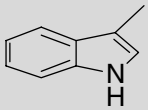
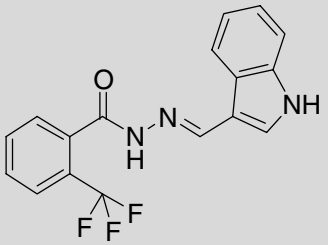
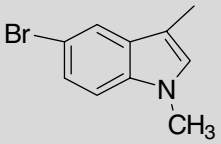
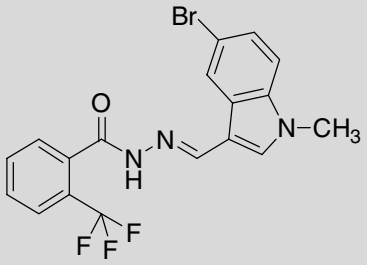
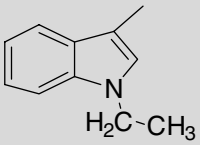
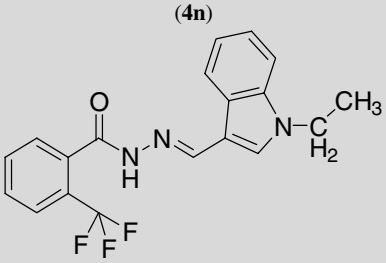
Fig. 3. Pyrazole hydrazides (**4s-4u**); **4s**: R = H; **4t**: R = OCH_3; **4u**: R = Cl

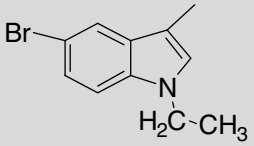
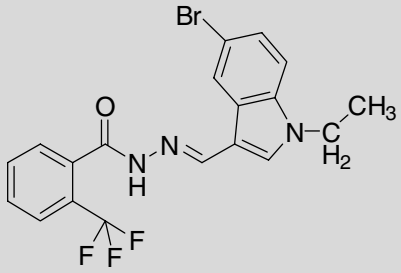
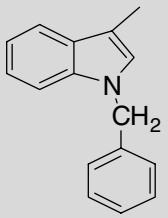
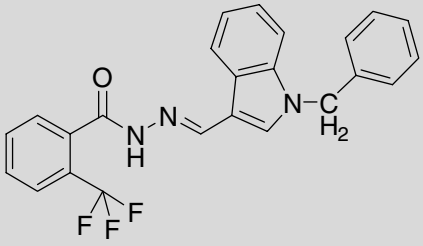
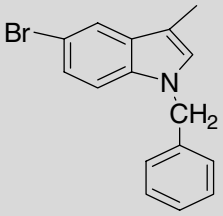
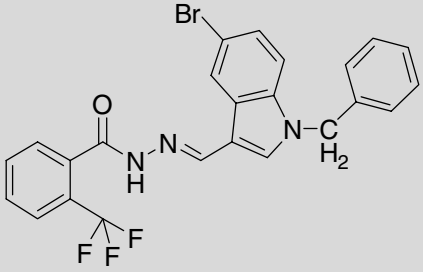
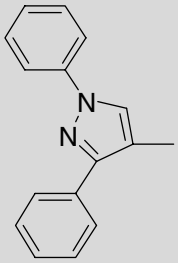
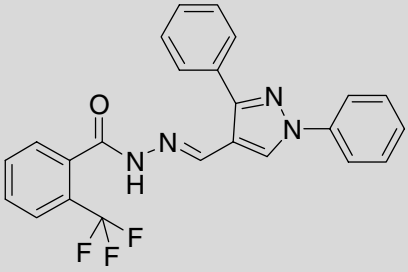
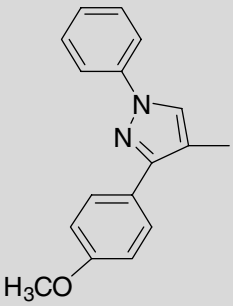
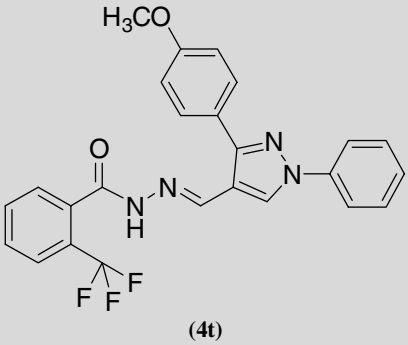
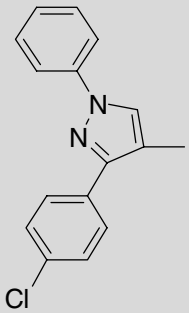
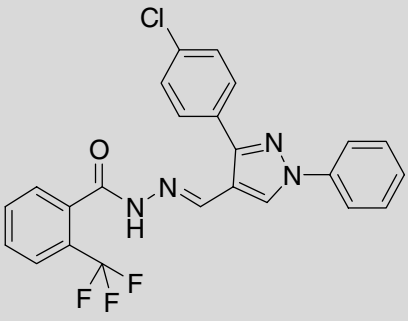
The conversion of 2-trifluoromethyl benzoic acid (**1**) into its ethyl ester (**2**) is a well known process and obtained the yields around 99 %. In the second stage the ester compound **2** was converted into 2-(trifluoromethyl)benzohydrazide (**3**) with a reasonable yield of 60-70 % by vigorous reflux in acetic acid and hydrazine hydride for about 6 h. Finally, the compounds (**4a-4u**) were prepared by condensing intermediate (**3**) with various aldehydes with good purity and greater than 90 % yields. All the compounds were characterized by their ^{1}H NMR, ^{13}C NMR and Mass spectral analysis, melting points were recorded on remi 125 melting point apparatus.

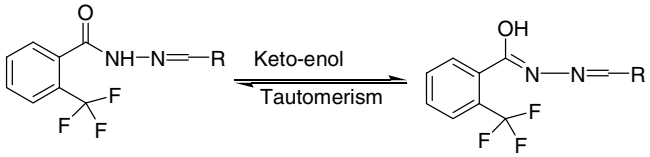
An observation on the NMR spectra indicated the formation of keto-enol tautomerism (**Scheme-II**) in the products synthesized. Moreover, the ratio of keto-enol forms were depend on the substituent's present on the R attached to double bonded carbon. Compound **4a** in which R is only phenyl group NMR showed that keto-enol forms ratios are (57:43) and compound **4b** with R is *p*-hydroxy phenyl, the NMR reveals that keto-enol forms ratios are (61:39) and if R is having N-ethyl, 5-Br indol **(4p)** the keto-enol forms are (65:35). If R is having a withdrawing group like *o*-NO_2 **(4h)** and *p*-NO_2 **(4c)** on phenyl NMR showed that keto-enol forms are in equal ratios (50:50). The above results clearly indicate that compounds

TABLE-1
SYNTHETIC DATA OF 2-(TRIFLUOROMETHYL)BENZOHYDRAZIDE DERIVATIVES

Entry	R	Product	Time (h)	Yield (%)	m.p. (°C)
1		 **(4a)**	2.5	96	138-140
2		 **(4b)**	3	91	240-242
3		 **(4c)**	3	96	176-178
4		 **(4d)**	2.5	97	148-150
5		 **(4e)**	3	92	196-198
6		 **(4f)**	3	95	172-174
7		 **(4g)**	2.5	96	158-160
8		 **(4h)**	2.5	96	159-161

9		 (**4i**)	2.5	94	149-151
10		 (**4j**)	3	95	163-165
11		 (**4k**)	2.5	96	144-146
12		 (**4l**)	3	94	158-160
13		 (**4m**)	2.5	96	230-232
14		 (**4n**)	3	92	180-182
15		 (**4o**)	3	94	155-157

16		 **(4p)**	3	92	160-162
17		 **(4q)**	2.5	95	208-210
18		 **(4r)**	2.5	91	173-176
19		 **(4s)**	3	97	106-108
20		 **(4t)**	3	95	176-178
21		 **(4u)**	3	96	156-158



Scheme-II: R = pheny/aryl/indolyl/substituted indol/substituted pyrazole

having electron withdrawing groups on (R) gave high enol form compared to compounds with electron donating substituents.

Conclusion

A series of three different types of biologically important 21 novel benzohydrazide derivatives (**4a-4u**) were synthesized by condensing the 2-(trifluoromethyl)benzohydrazide with various aldehydes in ethanol potassium hydroxide medium with good purity and high yields. The NMR spectra revealed that the synthesized compounds showed keto-enol tautomerism. By observing the different keto-enol ratios in NMR spectra of various substituents it clearly indicated that compounds having electron withdrawing groups on (R) gave high enol form compared to the compounds with electron donating groups.

ACKNOWLEDGEMENTS

The authors are highly thankful to Acharya Nagarjuna University and UGC for providing financial support (BSR Meritorious Fellowship [F.4-1/2006(BSR)/11-67/2008(BSR) dt. 22.10.2013]) and constant encouragement.

REFERENCES

1. A.P. Rajput and S.S. Rajput, *Int. J. Pharm. Pharm. Sci.*, **3**, 346 (2011).
2. R. Kalsi, M. Shrimali, T.N. Bhalla and J.P. Barthwal, *Indian J. Pharm. Sci.*, **41**, 353 (2006).
3. Y.S. Rao, I. Aminul, D. Nageswar and B.H. Babu, *Indian J. Chem.,* **54B**, 1162 (2015).
4. Y. Janin, *Bioorg. Med. Chem.*, **15**, 2479 (2007).
5. S.R. Yatcherla, A. Islam, D. Nageswar and B.H. Babu, *Asian J. Chem.*, **27**, 3729 (2015).
6. E. Gürsoy and N.U. Güzeldemirci, *Eur. J. Med. Chem.*, **42**, 320 (2007).
7. Y.S. Rao, I. Aminul, D. Nageswar and B.H. Babu, *Int. J. Curr. Res. Chem. Pharma. Sci.*, **2**, 25 (2015).
8. L. Savini, L. Chiasserini, V. Travagli, C. Pellerano, E. Novellino, S. Cosentino and M.B. Pisano, *Eur. J. Med. Chem.*, **39**, 113 (2004).
9. S. Sundriyal, R.K. Sharma and R. Jain, *Curr. Med. Chem.*, **13**, 1321 (2006).
10. T.R. Li, Z.Y. Yang and B.D. Wang, *Chem. Pharm. Bull. (Tokyo)*, **55**, 26 (2007).
11. G. Sammaiah and M. Sarangapani, *Asian J. Chem.*, **20**, 282 (2008).
12. G. Sammaiah and M. Sarangapani, *Int. J. Chem. Sci.*, **6**, 503 (2008).
13. G. Sammaiah and M. Sarangapani, *Int. J. Chem. Sci.*, **5**, 181 (2007).
14. C.G. Wermuth, *J. Med. Chem.*, **47**, 1303 (2004).
15. G. Kumar, D. Kumar, S. Devi, R. Johari and C.P. Singh, *Eur. J. Med. Chem.*, **45**, 3056 (2010).
16. S. Gemma, G. Kukreja, C. Fattorusso, M. Persico, M. Romano, M. Altarelli, L. Savini, G. Campiani, E. Fattorusso, N. Basilico, D. Taramelli, V. Yardley and S. Butini, *Bioorg. Med. Chem. Lett.*, **16**, 5384 (2006).
17. P. Singh and P.K. Jangra, *Der Chemica Sinica*, **1**, 118 (2010).
18. V. Singh, V.K. Srivastava, G. Palit and K. Shanker, *Arzneim-Forsch. Drug Res.*, **42**, 993 (1992).
19. G. Turan-Zitouni, M.F. Sivaci, S. Kilic and K. Erol, *Eur. J. Med. Chem.*, **36**, 685 (2001).
20. O. Bekircan, M. Küxük, B. Kahveci and S. Kolaylý, *Arch. Pharm.*, **338**, 365 (2005).
21. B.E. Gilbert and V. Knight, *Antimicrob. Agents Chemother.*, **30**, 201 (1986).
22. K. Akiba and M. Wada, *Chem. Abstr.*, **111**, 96964b (1989).
23. N. Ramalakshmi, R. Vijayakumar, K. Ilango, S. Arunkumar and A. Puratchikody, *Int. J. Chem. Sci.*, **6**, 1213 (2008).
24. S.D. Young, S.F. Britcher, L.O. Tran, L.S. Payne, W.C. Lumma, T.A. Lyle, J.R. Huff, P.S. Anderson, D.B. Olsen and S.S. Carroll, *Antimicrob. Agents Chemother.*, **39**, 2602 (1995).
25. B.D. Roth, *Prog. Med. Chem.*, **40**, 1 (2002).
26. K.-H. Ahn, H. Kim, J.R. Kim, S.C. Jeong, T.S. Kang, H.T. Shin and G.J. Lim, *Bull. Korean Chem. Soc.*, **23**, 626 (2002).
27. D.T. Wong, J.S. Horng, F.P. Bymaster, K.L. Hauser and B.B. Molloy, *Life Sci.*, **15**, 471 (1974).
28. P. Schlagenhauf, *Travel Med.*, **6**, 122 (1999).