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RESEARCH ARTICLE

Synthesis and Characterization of Some Pharmaceutically important N'-Benzylidene-2-(3-(3-Isopropoxy-5-(Trifluoromethyl)Phenyl)-1H-1,2,4-Triazol-1-yl)-Acetohydrazides

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ABSTRACT

A series of fifteen novel analogues of 1H-1,2,4-triazole derivatives were synthesized. The targeted 1H-1,2,4-triazoles were prepared by reacting 1H-1,2,4-triazolylacetohydrazide with various substituted benzaldehydes in the presence of acid catalyst. Various reaction conditons were tried to optimize the product yields. The structures of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, 1H NMR, 13C NMR spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and NMR analysis technique.

KEYWORDS

Acetohydrazide, Schiff-base, 1H-1,2,4-triazole

INTRODUCTION

The synthesis and biological applications of heterocyclic compounds is well explained with the progressive conclusion in literature. Among these heterocycles, 1,2,4-triazoles are prominent due to their diverse agricultural, industrial and biological activities. A lot of articles including synthesis and pharmacological applications of 1,2,4-triazoles have been published in the past few years[1-9]. Structures and biological activities of some pharmaceutically useful 1,2,4-triazole derivatives are shown in Figure 1. Thus with an effort to capitalize the biological potential of the 1,2,4-triazoles and to provide more interesting compounds for biological screening, the synthesis of a series of 1,2,4-triazole Schiff-base have undertaken and reported here in.

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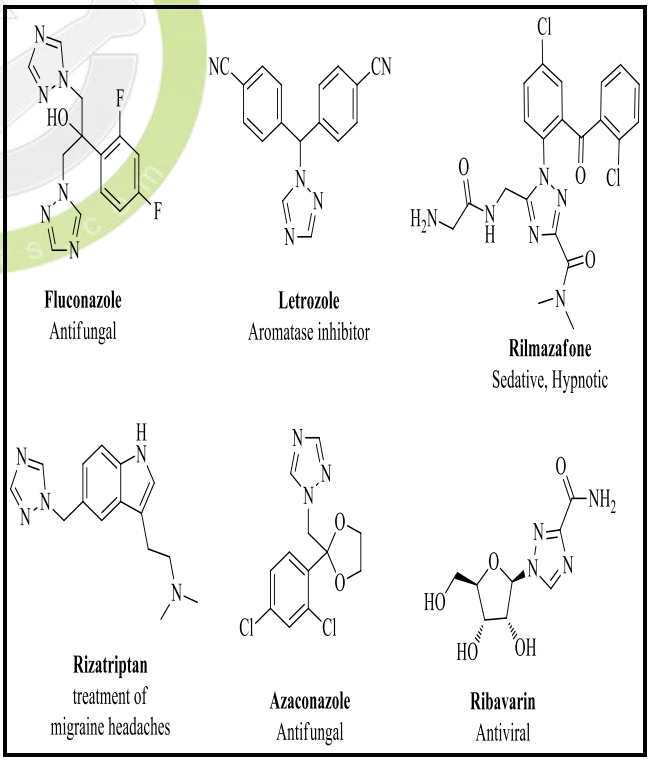
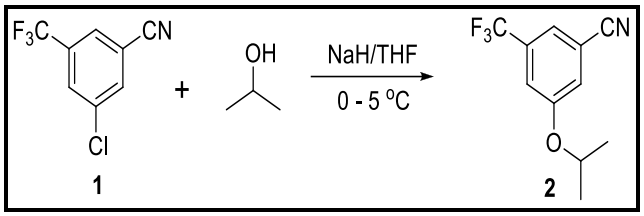


Figure 1: Pharmaceutically Important 1,2,4-triazole

Experimental Procedure

All chemicals and solvents were purchased from Spectrochem Pvt Ltd., Mumbai of AR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS prob KBr pallet. 1H-NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400MHz) DMSO6 solvent. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

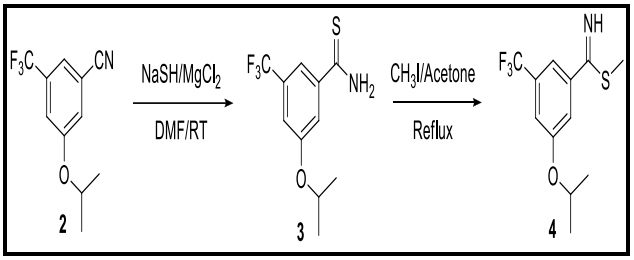
Synthesis of 3-isopropoxy-5-(trifluoromethyl) benzonitrile (2)



In a 250-ml one neck RBF, a mixture of isopropyl alcohol (4.2 g, 70 mmol) in THF (20 mL) was added to a suspension of NaH (1.44 g, 60 mmol) in THF (100 mL). Resulting mixture was allowed to stir at RT for 3h. 3-chloro-5-(trifluoromethyl)benzonitrile **1** (10.2 g, 50 mmol) in THF (80 mL) was added in the above reaction mixture in dropwise manner at 0°C and temperature was maintained the same for 30 min. Completion of reaction was then conformed by TLC. Resulting reaction mixture was then poured in ice water and extracted with ethyl acetate. Organic layer was separated and washed with water, dried over anhydrous Na_2SO_4 and filtered. Filtrate was then concentrated by rotary evaporation to afford a crude 3-isopropoxy-5-(trifluoromethyl)benzonitrile **2** as yellow oil (Yield: 8.0 g, 70 %).

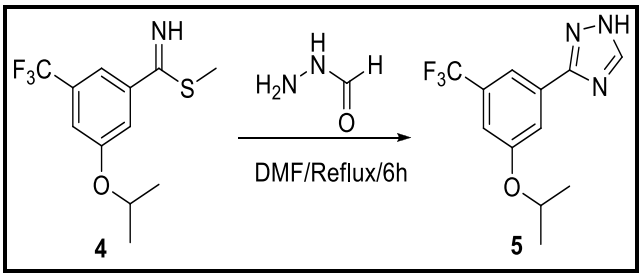
Synthesis of methyl 3-isopropoxy-5-(trifluoromethyl)benzimidothioate (4)

In a 500 mL 3N RBF, attached with nitrogen bubbler & magnetic stirrer, 3-isopropoxy-5-(trifluoromethyl)benzonitrile 2 (7.5 g, 32.5 mmol), NaSH (2.8 g, 50 mmol), $MgCl_2$ (9.5 g, 100 mmol) was dissolved/suspended in DMF (75 mL) at RT. Resulting mixture was stirred at RT for 3h.The Completion of the reaction was confirmed by TLC (EtOAc:Hexane/2:8). Reaction mixture was then poured in ice-water and extracted with ethylacetate (50 mL × 3). Organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to afford a crude 3-isopropoxy-5-(trifluoromethyl) benzothioamide 3 as yellow oil (Yield: 7.9 g, 92%). The obtained crude product was used for next step without purification.



In a 250 mL 3N RBF, attached with nitrogen bubbler & magnetic stirrer, obtained 3-isopropoxy-5-(trifluoromethyl)benzothioamide 3 (7.9 g, 30 mmol) was dissolved in acetone (55 mL) and CH3I (10.18 g) was added in a dropwise manner at RT. Reaction mixture was then refluxed for 2h.The Completion of the reaction was confirmed by TLC (Acetone:Hexane/2:8). Resulting mixture was then evaporated to dryness to obtain methyl 3-isopropoxy-5-(trifluoromethyl) benzimidothioate 4 as crude oily material, which was used for next step without further purification.

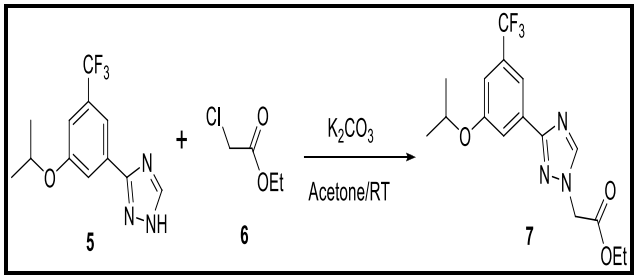
Synthesis of 3-(3-isopropoxy-5-(trifluoromethyl) phenyl)-1H-1,2,4-triazole (5)



In a 250 mL 3 neck RBF, methyl 3-isopropoxy-5-(trifluoromethyl)benzimidothioate 4 (5.54 g, 20 mmol) was dissolved in DMF (50 mL) and formic hydrazide (2.4 g, 40 mmol) was added.

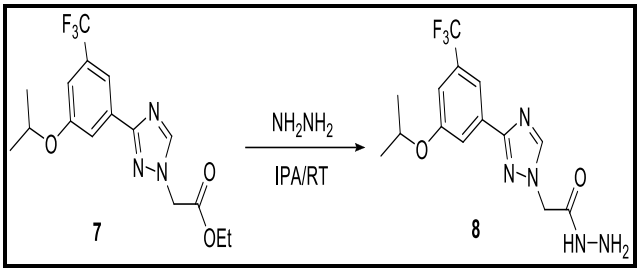
Resulting mixture was then stirred at RT for 30 to form uncyclised intermediate form, which was confirmed by mass & on TLC as a polar spot as compared to SM 3. Reaction mixture was then refluxed at 90 oC for 6 h and the progress of the reaction was monitored by TLC using (Ethyl acetate:Hexane/5:5). Reaction mixture was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate (200 mL × 3). The combined organic layer was washed with brine solution, dried over anhydrous Na2SO4, filtered and filtrate was concentrated using rotary evaporation under reduced pressure. Obtained crude product was then purified by column chromatography using ethyal acetate:hexane (25:75) as mobile phase. The fraction containing main product was then combined and evaporated in rotary evaporator to obtain the pure 3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole 5 as pale yellow solid (Yield: 4.5 g, 83%).

Synthesis of ethyl 2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetate (7)



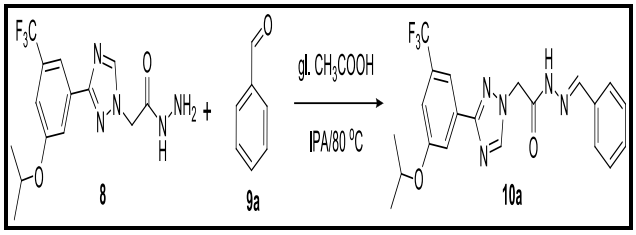
In a 250 mL RBF, a mixture of 3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole **5** (2.71 g, 10 mmol) and anhydrous K_2CO_3 (2.6 g) in dry acetone (25 mL) was stirred at room temperature and was added ethyl chloroacetate **6** (1.2 mL, 11 mmol) dropwise. The reaction mixture was stirred for 8 h at room temperature (TLC System: $CHCl_3$:MeOH/9:1, Rf: 0.65). The resulting solution was then evaporated in vacuum and solid obtained was suspended in cold water with stirring, which was then filtered. The solid filtered was successively washed with water followed by hexane and dried in vacuum to give desired ethyl 2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetate **7** (Yield: 3 g, 85%); MP: 173–174ºC.

Synthesis of 2-(3-(3-isopropoxy-5-(trifluoromethyl) phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide (8)



In a 250 mL single neck RBF, a solution of ethyl 2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetate **7** (3.57 g, 10 mmol) was prepared in isopropyl alcohol (30 mL). To this solution, hydrazine hydrate (98%, 5 mL) was added with vigorous stirring and resulting mixture was continuously stirred at room temperature for 1 h. After the completion of reaction as indicated by TLC ($CHCl_3$:MeOH/9:1, Rf: 0.4), solid separated was filtered and washed with cold IPA to give 2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide **8** as white solid (2.9 g, 82%); MP: 246–248 ºC.

Synthesis of N'-benzylidene-2-(3-(3-isopropoxy-5-(trifluoromethyl) phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide (10a)



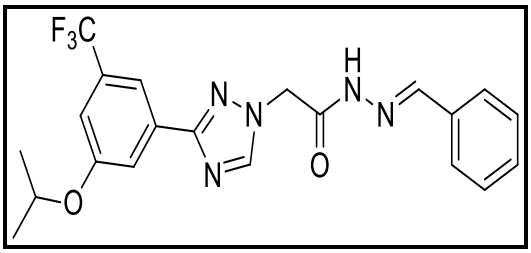
In a 100 ml single neck RBF, 2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide **5** (0.86 g, 2 mmol) was dissolved in isopropyl alcohol (30 mL) and benzaldehyde **9a** (0.23 g, 2.2 mmol) was added followed by few drops of gla. CH_3COOH. The reaction mixture was then stirred at room temperature for 1 h. After completion of the reaction as monitored by TLC ($CHCl_3$:MeOH/9:1, Rf: 0.52), solution was poured in ice water and stirred for 30 min at room temperature. Solid separated was then filtered and washed with water followed by IPA

to give pure N'-benzylidene-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide **10a** as white solid (Yield: 0.86 g, 92%); MP: 182–183 ºC.

By following the method described for the synthesis of compound PCL-201, remaining triazole-Schiff-base PCL-202 to PCL-215 were prepared in good yield. The physical as well as analytical data of these derivatives are given bellow.

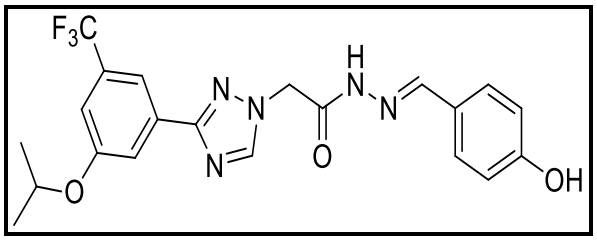
Experimental Data Table

N'-benzylidene-2-(3-(3-isopropoxy-5-(trifluoro-methyl)phenyl)-1H-1,2,4-triazol-1-yl) aceto-hydrazide 10a



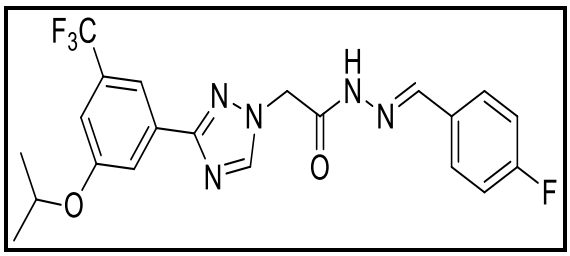
^{1}H NMR (400 MHz, DMSO) δ 11.91 (s, 1H, NH), 8.78 (d, *J* = 12.3 Hz, 1H, ArH), 8.52 (s, 2H, ArH), 8.24 (d, *J* = 12.7 Hz, 1H, ArH), 8.07 (s, 1H, ArH), 7.80 – 7.70 (m, 2H, ArH), 7.46 – 7.50 (m, 3H), 5.66 (s, 2H, CH_2), 4.78 – 4.84 (m, 1H, CH), 1.33 and 1.31 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.6, 160.3, 158.5, 147.75, 143.78, 133.23, 133.14, 132.68, 131.70, 130.32, 129.84, 124.44, 119.01, 114.4, 109.72, 71.01, 50.55, 21.5; M.P. 182-183 ºC

N'-(4-hydroxybenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10b



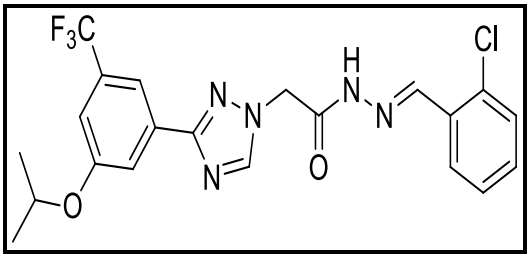
^{1}H NMR (400 MHz, DMSO) δ 11.84 (s, 1H, NH), 11.20 (brs, 1H, OH), 8.70 (s, 1H, ArH), 8.16 (s, 1H, ArH), 7.96 (s, 1H, ArH), 7.74 (s, 1H, ArH), 7.53 – 7.59 (m, 2H, ArH), 7.28 (s, 1H, ArH), 6.82 – 6.85 (m, 2H, ArH), 5.56 (s, 2H,CH_2), 4.77 – 4.83 (m, 1H, CH), 1.32 and 1.30 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.3, 161.5, 158.2, 147.2, 144.8, 139.4, 133.3, 131.5, 131.0, 131.1, 129.7, 128.7, 125.10, 123.5, 115.9, 113.7, 113.0, 70.2, 50.3, 21.5; M.P. 186–187ºC

N'-(4-fluorobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10c



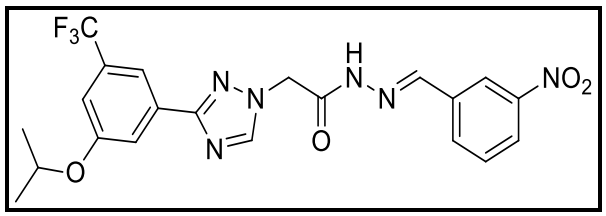
^{1}H NMR (400 MHz, DMSO) δ 11.91 (s, 1H, NH), 8.82 – 8.67 (m, 1H, ArH), 8.49 (s, 2H, ArH), 8.22 (d, *J* = 8.4, 1H, ArH), 8.05 (s, 1H, ArH), 7.98 – 7.73 (m, 2H, ArH), 7.28 (t, *J* = 8.6 Hz, 2H, ArH), 5.65 (s, 2H, CH_2), 4.75 – 4.76 (m, 1H, CH), 1.32 and 1.34 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.8, 162.5, 158.1, 147.7, 143.6, 143.1, 134.5, 132.7, 131.8, 131.2, 130.8, 128.4, 124.4, 121.3, 116.2, 109.2, 71.1, 50.8, 21.9; M.P. 203-204 ºC

N'-(2-chlorobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10d



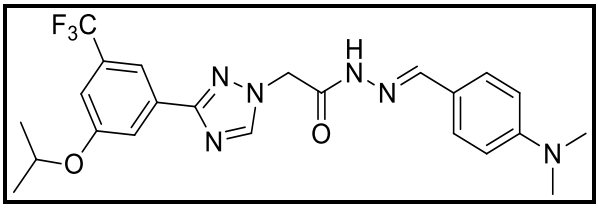
^{1}H NMR (400 MHz, DMSO) δ 12.11 (s, 1H, NH), 8.78 (m, 1H, ArH), 8.52 – 8.49 (m, 3H, ArH), 8.16 (s, 1H, ArH), 8.00 – 7.97 (m, 1H, ArH), 7.56 – 7.36 (m, 3H, ArH), 5.67 (s, 2H, CH_2), 4.78 – 4.82 (m, 1H, CH), 1.29 and 1.31 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.6, 162.3, 158.5, 143.8, 139.5, 134.5, 133.2, 133.1, 132.8, 132.0, 131.7, 130.8, 127.6, 126.9, 124.4, 119.0, 116.4, 112.7, 109.8, 71.0, 50.5, 29.1; M.P. 212-213 ºC

N'-(3-nitrobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10e



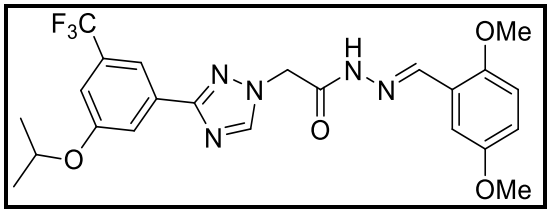
^{1}H NMR (400 MHz, DMSO) δ 12.18 (s, 1H, NH), 8.82 (s, 1H, NH), 8.50 – 8.47 (m, 3H, ArH), 8.21 (d, J = 4.4 Hz, 2H, ArH), 8.17 – 8.04 (m, 1H, ArH), 7.83 (t, J = 7.3 Hz, 1H, ArH), 7.71 (t, J = 7.3 Hz, 1H, ArH), 5.70 (s, 2H, CH_2), 4.78 – 4.82 (m, 1H, CH), 1.30 and 1.31 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.8, 163.5, 158.2, 150.8, 147.5, 143.2, 140.9, 135.7, 132.5, 132.4, 130.8, 129.6, 126.9, 124.2, 121.5, 117.1, 114.5, 109.8, 70.8, 51.2, 28.8; M.P. 235-236 ºC.

N'-(4-(dimethylamino)benzylidene)-2-(3-(3-iso propoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10f



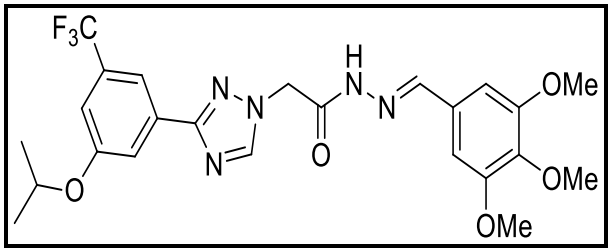
^{1}H NMR (400 MHz, DMSO) δ 12.12 (s, 1H, NH), 8.76 (d, *J* = 14.1 Hz, 1H), 8.51 – 8.48 (m, 3H), 8.14 (s, 1H, ArH), 8.02 – 7.98 (m, 1H, ArH), 7.54 – 7.34 (m, 3H, ArH), 5.63 (s, 2H,CH_2), 4.78 – 4.84 (m, 1H, CH), 3.18 (s, 6H, N-Me_2), 1.33 and 1.31 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 168.6, 161.3, 158.4, 153.1, 147.7, 143.8, 133.1, 132.9, 131.6, 131.4, 129.8, 125.4, 122.4, 121.7, 117.9, 111.9, 109.8, 70.8, 51.1, 21.8; M.P. 166-167ºC

N'-(2,5-dimethoxybenzylidene)-2-(3-(3-isopro poxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10g



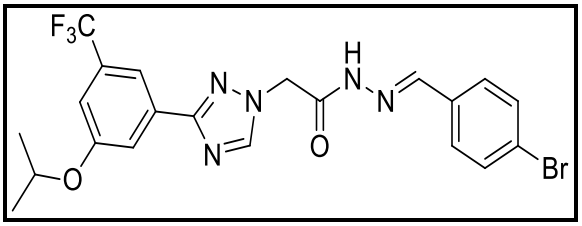
^{1}H NMR (400 MHz, DMSO) δ 11.84 (s, 1H, NH), 8.68 (s, 1H, ArH), 8.38 (s, 1H, ArH), 7.83 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.45 – 7.46 (m, 1H, ArH), 7.28 (s, 1H, ArH), 7.00 – 7.07 (m, 2H, ArH), 5.65 (s, 2H,CH_2), 4.78 – 4.84 (m, 1H, CH), 3.81 and 3.74 (s, 6H, OCH_3), 1.33 and 1.31 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.5,162.1, 159.4, 158.2, 153.2, 152.1, 147.3, 139.8, 133.4, 131.1, 125.1, 122.3, 119.7, 117.8, 117.4, 115.7, 113.8, 113.6, 109.5, 70.1, 56.0, 55.4, 50.8, 21.5; M.P. 222-223ºC

N'-(3,4,5-trimethoxybenzylidene)-2-(3-(3-iso propoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10h



^{1}H NMR (400 MHz, DMSO) δ 11.92 (s, 1H, NH), 8.69 (s, 1H, ArH), 8.20 (s, 1H, ArH), 7.99 (m, 1H, ArH), 7.82 (s, 1H, ArH), 7.76 (s, 1H, ArH), 7.28 (s, 1H, ArH), 7.04 – 7.08 (m, 2H, ArH), 5.65 (s, 2H,CH_2), 4.80 – 4.84 (m, 1H, CH), 3.71, and 3.83 (s, 6H, 2×OCH_3), 1.31 and 1.33 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.5, 162.2, 158.2, 153.2, 147.7, 146.6, 143.2, 133.1, 132.7, 131.1, 128.8, 125.5, 124.4, 121.7, 116.9, 113.8, 106.8, 70.9, 60.5, 55.2, 51.9, 21.8; M.P. 194-196 ºC

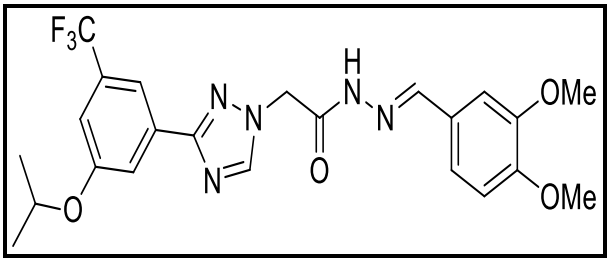
N'-(4-bromobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10i



^{1}H NMR (400 MHz, DMSO) δ 11.97 (s, 1H, ArH), 8.77 (d, J = 14.6 Hz, 1H, ArH), 8.50 (s, 2H, ArH), 8.21 (d, J = 14.6 Hz, 1H, ArH), 8.03 (s, 1H, ArH), 7.71 (d, J = 8.5 Hz, 2H, ArH), 7.65 (t, J = 6.0 Hz, 2H, ArH), 5.65 (s, 2H, CH_2), 4.84

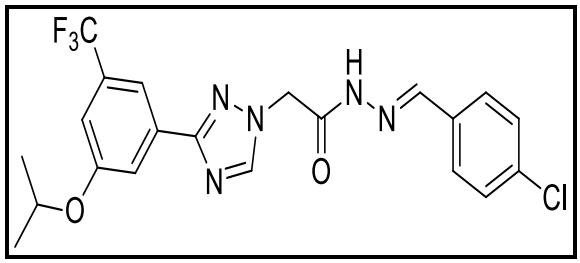
(m, 1H, CH), 1.33 and 1.30 (s, 6H, CH_3); ^{13}C NMR (100 MHz,DMSO) δ 167.3, 162.9, 158.7, 144.5, 143.8, 133.3, 132.8, 132.5, 131.7, 126.3, 125.6, 123.5, 116.3, 113.7, 110.5, 71.0, 51.9, 21.5.; FT—IR ν_{max} cm^{-1} 3061, 2970, 1681, 1602, 1498, 1406, 1354, 1315, 1238, 1172, 1109, 1041, 993, 933, 908, 835, 758, 704, 682, 661.; M.P. 205-206 °C

N'-(3,4-dimethoxybenzylidene)-2-(3-(3-iso propoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10j



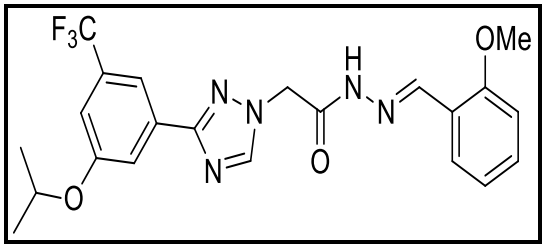
^1H NMR (400 MHz, DMSO) δ 11.79 (s, 1H, NH), 8.77 (d, J = 10.4 Hz, 1H, ArH), 8.49 (s, 2H, ArH), 8.17 (d, J = 6.7 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 7.35 – 7.33 (m, 1H, ArH), 7.22 (t, J = 8.5 Hz, 1H, ArH), 7.01 (t, J = 7.2 Hz, 1H, ArH), 5.66 (s, 2H, CH_2), 4.78 – 4.84 (m, 1H, CH), 3.82 and 3.80 (s, 6H, OCH_3), 1.35 and 1.34 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.6, 162.3, 158.5, 152.2, 147.7, 143.8, 140.5, 133.2, 131.7, 130.8, 127.6, 125.5, 122.4, 119.0, 116.9, 115.1, 111.5, 110.0, 70.23, 51.01, 50.55, 21.56; M.P. 179-180 °C

N'-(4-chlorobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10k



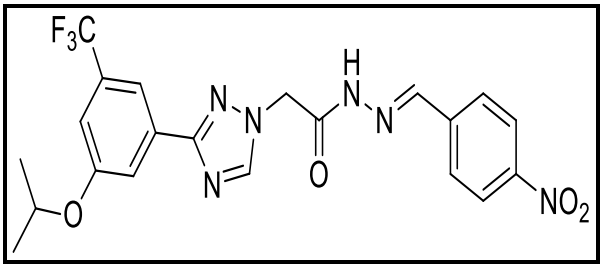
^1H NMR (400 MHz, DMSO) δ 11.97 (s, 1H, NH), 8.77 (m, 1H, ArH), 8.49 (s, 2H, ArH), 8.21 (m, 1H, ArH), 8.05 (s, 1H, ArH), 7.76 (d, J = 8.4 Hz, 2H, ArH), 7.50 (d, J = 8.4 Hz, 2H, ArH), 5.65 (s, 2H, CH_2), 4.75 – 4.76 (m, 1H, CH), 1.32 and 1.34 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.5, 162.2, 158.2, 147.7, 143.8, 143.2, 134.7, 132.7, 131.8, 131.1, 130.8, 128.83, 124.44, 121.73, 116.2, 110.2, 71.0, 50.98, 21.9; M.P. 234-235 °C

N'-(2-methoxybenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10l



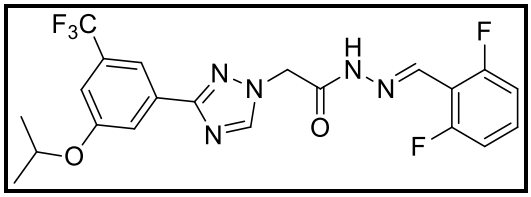
^1H NMR (400 MHz, DMSO) δ 11.89 (s, 1H, ArH), 8.78 (d, J = 13.9 Hz, 1H, ArH), 8.57 – 8.55 (m, 2H, ArH), 8.41 (s, 1H, ArH), 8.21 (s, 1H, ArH), 7.86 (d, 7.1 Hz, 1H, ArH), 7.44 (d, J = 7.2 Hz, 1H, ArH), 7.12 (d, J = 8.1 Hz, 1H, ArH), 7.07 – 6.93 (m, 1H, ArH), 5.65 (s, 2H, CH_2), 4.71 – 4.73 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 1.41 and 1.42 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.8, 162.6, 158.2, 157.6, 147.7, 142.1, 133.1, 131.6, 131.1, 130.8, 124.4, 121.7, 119.0, 116.5, 111.7, 110.0, 70.2, 50.9, 21.8; M.P. 186-187 °C

N'-(4-nitrobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10m



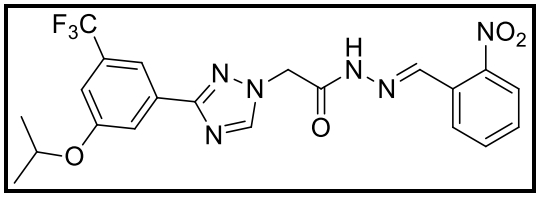
^1H NMR (400 MHz, DMSO) δ 11.70 (s, 1H, NH), 8.78 (s, 1H, ArH), 8.48 (s, 2H, ArH), 8.27 (d, J = 8.6 Hz, 2H, ArH), 8.16 (d, J = 8.6 Hz, 2H, ArH), 7.99 (t, J = 9.3 Hz, 2H, ArH), 5.70 (s, 2H, ArH), 4.75 – 4.81 (m, 1H, CH), 1.41 and 1.42 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 163.5, 157.9, 150.8, 147.5, 140.9, 140.8, 138.3, 135.7, 135.5, 132.4, 130.8, 127.7, 126.9, 126.3, 124.2, 115.9, 113.9, 109.6, 70.7, 50.9, 21.8; M.P. 256-257 °C

N'-(2,6-difluorobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide 10n



^{1}H NMR (400 MHz, DMSO) δ 11.50 (s, 1H, NH), 8.78 (d, J = 8.9 Hz, 1H, ArH), 8.50 (s, 2H, ArH), 8.20 (s, 2H, ArH), 7.62 – 7.45 (m, 1H, ArH), 7.22 (t, J = 8.7 Hz, 2H, ArH), 7.07 – 6.93 (m, 1H, ArH), 5.55 (s, 2H, CH_2), 4.71 – 4.73 (m, 1H, CH), 1.41 and 1.42 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.9, 161.0, 159.4, 158.3, 147.8, 142.1, 140.0, 133.1, 132.0, 131.9, 131.1, 130.8, 125.5, 124.4, 123.9, 121.7, 117.1, 114.0, 111.0, 70.9, 50. 7, 21.9; M.P. 199-200 ^{o}C

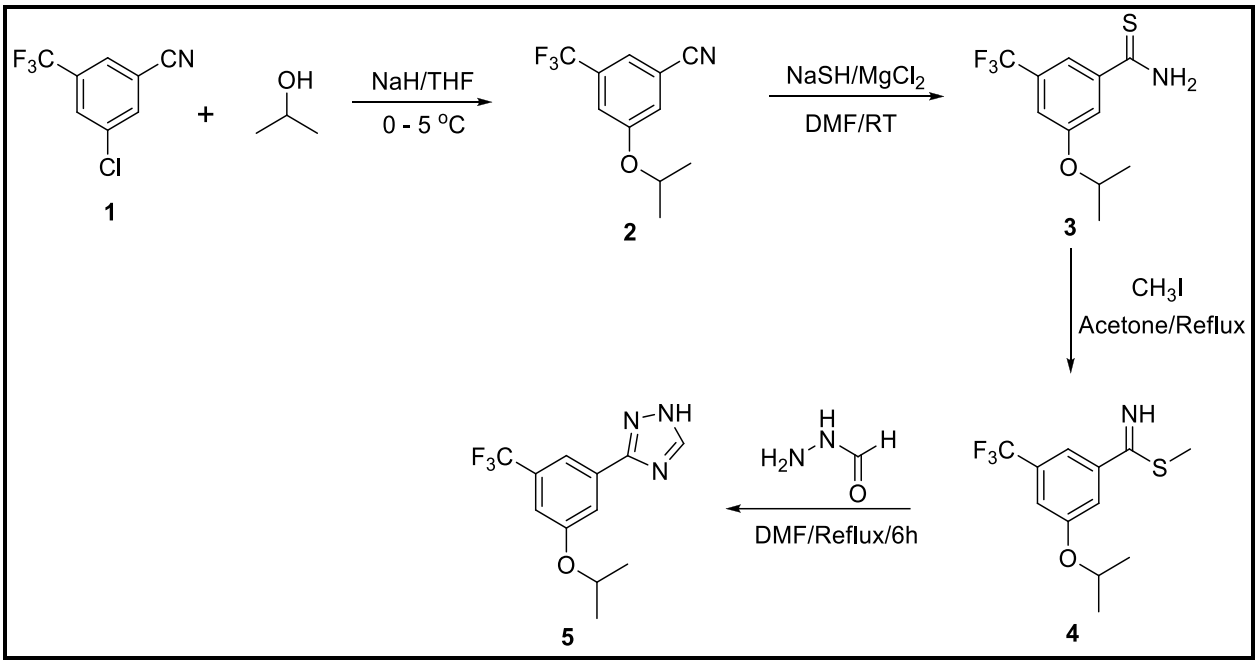
N'-(2-nitrobenzylidene)-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl) acetohydrazide 10o



^{1}H NMR (400 MHz, DMSO) δ 12.24 (s, 1H, NH), 8.77 (d, J = 8.4 Hz, 1H), 8.46 (m, 3H, ArH), 8.16 (d, J = 8.3 Hz, 2H, ArH), 8.12 – 7.99 (m, 1H), 7.79 (t, J = 7.3 Hz, 1H, ArH), 7.67 (t, J = 7.4 Hz, 1H, ArH), 5.66 (s, 2H, CH_2), 4.72 – 4.78 (m, 1H, CH), 1.37 and 1.38 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO) δ 167.4, 161.5, 159.0, 147.8, 143.1, 140.5, 134.8, 132.0, 131.9, 131.1, 130.8, 128.4, 124.7, 124.5, 124.4, 116.9, 112.4, 109.2, 70.1, 50.3, 21.5; M.P. 249-250 ^{o}C.

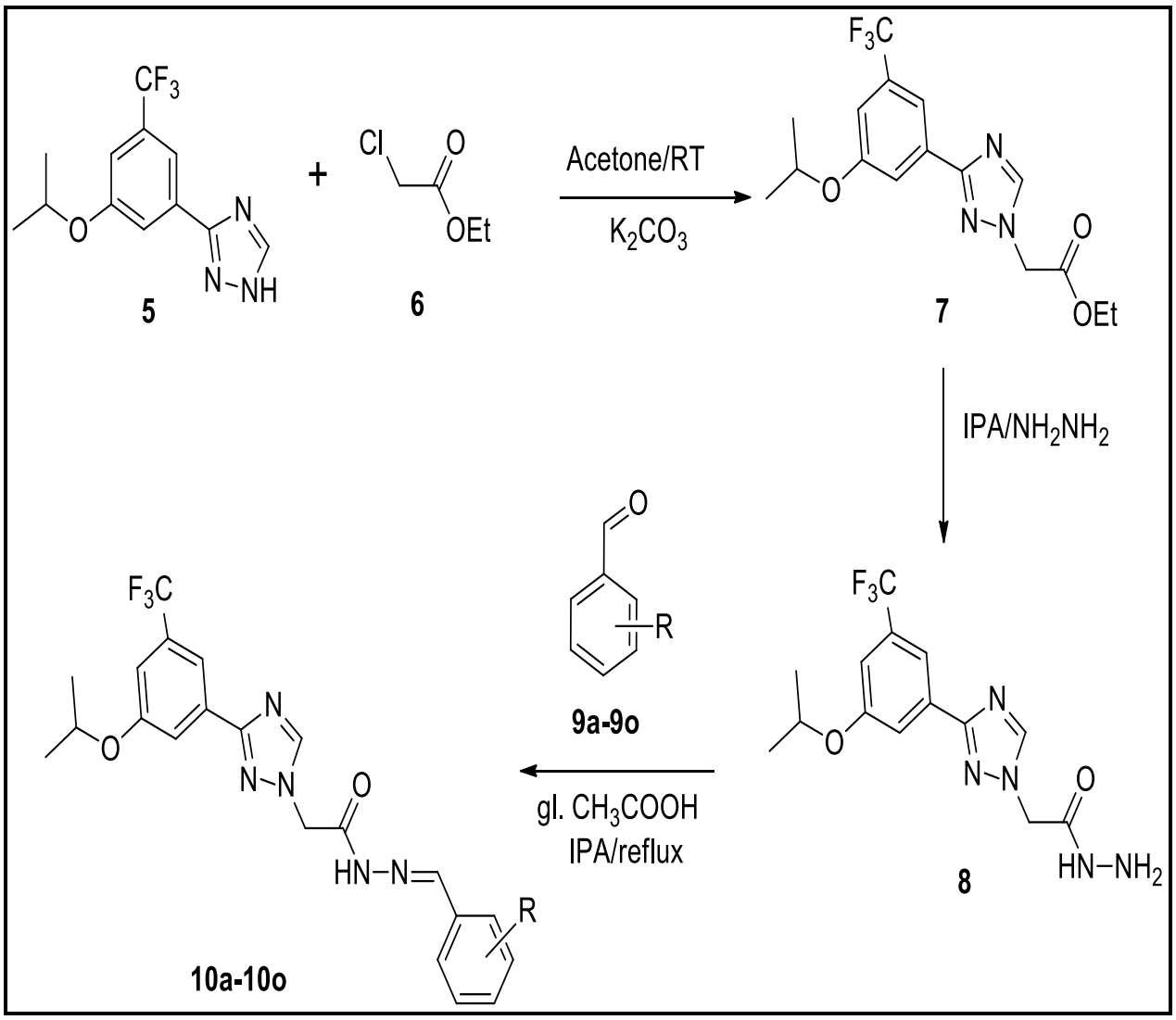
RESULTS AND DISCUSSION

Reaction Schemes



Scheme 1: Preparation of key starting materials

Synthesis of targeted substituted N'-benzylidene-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-acetohydrazide derivatives was achieved starting from 3-chloro-5-(trifluoromethyl)benzonitrile as depicted in Scheme 2. The optimization of the reaction condition for the targeted derivatives is described below.

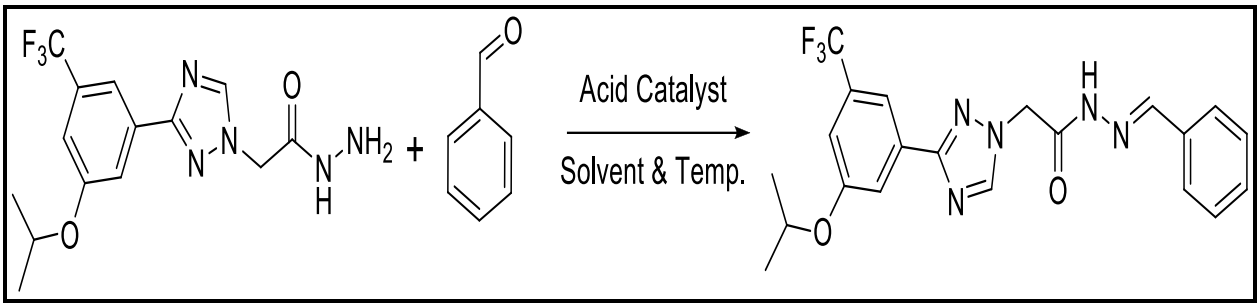


Scheme 2: Preparation of targeted 1,2,4-triazole-Schiff-base

Initially, 2-(3-(3-isopropoxy-5-(trifluoromethyl) phenyl)-1H-1,2,4-triazol-1-yl) aceto hydrazide **8** (1.0 eq.) and benzaldehyde **9** (1.1 eq.) were stirred without catalyst at room temperature in MeOH for 1 h. Both starting materials remain as such in the reaction mass and no reaction was observed (entry 1, Table 1). Subsequently, few drops of acetic acid as catalyst was added to the above reaction mixture and stirred at room temperature for 1h resulted in product formation with 30% yield, which was improved to 65% after refluxing the reaction mixture (entry 2 & 3, Talbe 1). Next, we optimized the reaction conditions in order to increase the yield.

Thus, different solvents and temperature were screened and the results are summarized (Table 1). It was found that IPA was the most superior solvent and reflux condition was the most effective in terms of the product yield (entry 5, Table 1.). Next, various other acid catalyst were tried to confirm the superiority of the gla. CH_3COOH as catalyst. The results demonstrated that none of the catalyst gave the better yield than that of gla. CH_3COOH. By utilizing the optimized condition, various Schiff base of 1,2,4-triazole derivatives **(10a-10o)** were synthesized by condensing various aldehydes (**9a-9o**) with 1H-1,2,4-triazolyl-acetohydrazide (**8**) (Table 2).

Table 1: Optimization of the reaction condition[a]

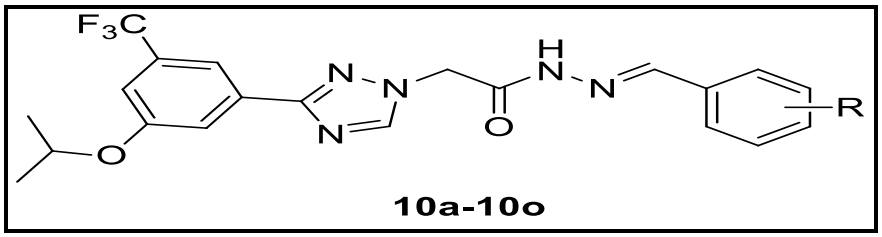


Entry	Catalyst	Solvent	Temp °C	time h	Yield[b] %
1	-	MeOH	RT	1	NR
2	Gla. CH_3COOH	MeOH	RT	1	30
3	Gla. CH_3COOH	MeOH	65	1	65
4	Gla. CH_3COOH	EtOH	80	1	80
5	Gla. CH_3COOH	IPA	80	1	92
6	Gla. CH_3COOH	MeCN	80	1	54
7	Gla. CH_3COOH	THF	80	1	62
8	Gla. CH_3COOH	$CHCl_3$	65	1	31
9	Gla. CH_3COOH	EtOAc	80	1	36
10	Gla. CH_3COOH	DMF	80	1	45
11	Con. HCl	IPA	80	1	65
12	CF_3COOH	IPA	80	1	75

[a]Reaction condition: 1H-1,2,4-triazolyl-acetohydrazide:benzaldehyde(1:1) + catalyst(few drops)

[b] isolated yields

Table 2: Physical data of the synthesized 1,2,4-triazole Schiff base derivatives



10a-10o

Entry	Code	R	Yield[b] (%)	mp °C
1	**10a**	H	92	182-184
2	**10b**	4-OH	93	186-187
3	**10c**	4-F	92	203-204
4	**10d**	2-Cl	79	212-213
5	**10e**	3-NO_2	90	235-236
6	**10f**	4-N,N-diMe	82	166-167
7	**10g**	2,5-diOMe	81	222-223
8	**10h**	3,4,5-triOMe	92	194-195
9	**10i**	4-Br	91	205-206
10	**10j**	3,4-diOMe	86	179-180
11	**10k**	4-Cl	87	234-235
12	**10l**	2-OMe	81	186-187
13	**10m**	4-NO_2	88	256-257
14	**10n**	2,6-diF	83	199-200
15	**10o**	2-NO_2	82	249-250

CONCLUSION

A series of substituted N'-benzylidene-2-(3-(3-isopropoxy-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)acetohydrazide have designed and synthesized in good to excellent yield. Suitable reaction condition for the synthesis of targeted compounds was studied. All the compounds are well characterized by various analytical techniques.

ACKNOWLEDGEMENT

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