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F(1*H*-Pyrazol-4-yl)methylene-Hydrazide derivatives: Synthesis and antimicrobial activity

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Abstract

This paper investigates the seismic and collapse performance of shape memory alloy (SMA) braced steel frame structures considering the effects of various brace design parameters and ultimate state of SMAs. An SMA braced steel frame building is designed to have comparable strength and stiffness with a steel-moment resisting frame selected as case study building. Then, the stiffness and ultimate deformation capacity of the SMA braces in the initially designed reference SMA braced frame are systematically varied. First, the static pushover analysis and incremental dynamic analysis (IDA) are employed to illustrate the significance of SMA brace failure consideration in seismic performance assessment of steel frames with SMA elements. Then, the influence of SMA brace initial stiffness and ultimate deformation capacity on the seismic and collapse performance of SMA braced frames are studied through pushover analyses, nonlinear response history analyses, and IDA. The results show that the SMA brace initial stiffness does not affect the interstory drift and floor absolute acceleration response at design and maximum considered earthquake (MCE) level seismic hazard or collapse capacity of the frame. However, it has considerable influence on post-event functionality of the frame. It is also found that the SMA brace ultimate deformation capacity should be at least 80% of maximum inter-story drift demand at MCE level for satisfactory seismic performance, while larger values provide higher collapse capacity for the SMA braced frame.

1 | INTRODUCTION

Heterocycles are core structures in numerous pharmaceutical compounds, wherein pyrazole derivatives received wide spread interest in medicinal and pesticide chemistry.[1] Several pyrazole derivatives are confirmed to be associated with various biological properties such as anti-inflammatory,[2] anti-microbial,[3] antitumor,[4] antileukemia,[5] antidepressant,[6] anti-convulsant,[7] antifungal,[8] anti-pyretic and analgesic[9] activities.

In recent times, aryl group containing pyrazoles have been disclosed to express non nucleoside HIV-1 inverse transcriptase inhibitor activity.[10] As potential clinically beneficial compounds, comprehensive studies have been dedicated towards aryl pyrazole derivatives such as the famous COX-2 inhibitor Celecoxib (Figure 1)[11–15] is revealed to be effective gastrointestinal (GI) safe analgesic and antiinflammatory agent. Deracoxib (Figure 1) is an anti-inflammatory non steroidal drug of the coxib class, used to treat osteoarthritis in dogs as veterinary

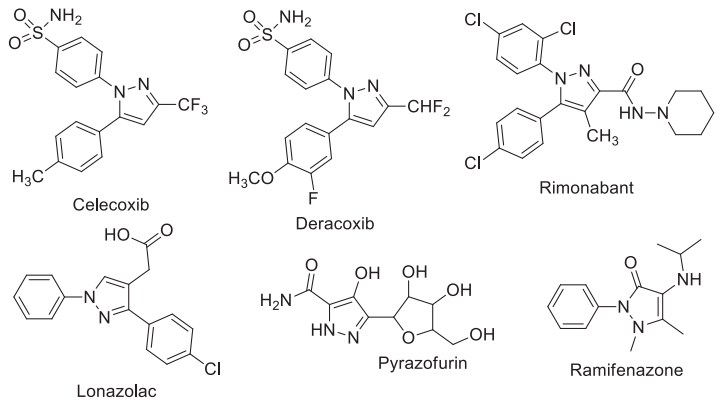


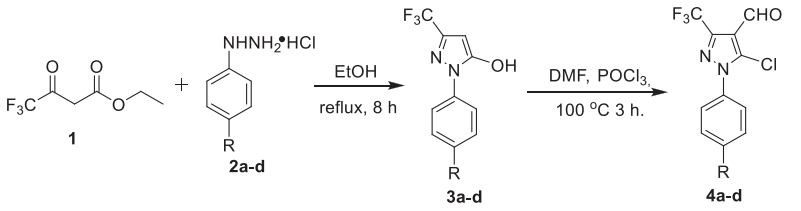
FIGURE 1 Commercially available drug candidate containing pyrazole nucleus

medicine.[16] Rimonabant (Figure 1) is the first selective CB1 receptor blocker and has been used as an antiobesity drug until 2009.[17] Then, this drug was withdrawn by the European Medicines Agency because of its side effects. Later on the innovation of the natural pyrazole C-glycoside and pyrazofurin (Figure 1) which established a wide spectrum of antimicrobial activity[18,19] much interest is given to pyrazoles as antimicrobial agents. In addition, pyrazoles with potential anti-MAO efficacy[20,21] and their analogues which represent inhibitors of *Mycobacterium tuberculosis*,[22] antitubercular agents,[23] FMS-like tyrosine kinase-3 (FLT3) inhibitors.[24] In Continuation of our study on the activity of pyrazoles against bacteria,[25–27] in this work, we would like to report the preparation of a variety of pyrazol-methylene-hydrazide derivatives and their antimicrobial activity study.

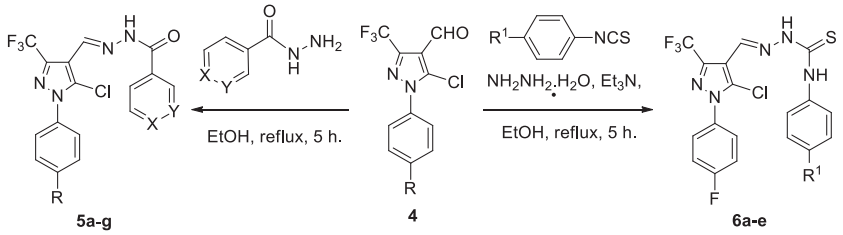
2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The direction used for the preparation of the pyrazole derivatives **5a-g** and **6a-e** assessed for this study is exposed in Scheme 1 and 2. The reaction of equimolar amounts of aryl hydrazine-hydrochloride **2a-d** and Ethyl 4,4,4-trifluoro-3-oxobutanoate **1** in absolute ethanol under reflux condition furnish the analogous of pyrazol-5-ols **3a-d** Then the reaction of pyrazol-5-ols **3a-d**, by Phosphoryl trichloride in *N*,*N*-Dimethyl formamide lead towards the formation of related 1*H*-Pyrazol-4-carbalehyde **4a-d**. Novel pyrazole derivatives **5a-g** were synthesized by the reaction of 1*H*-pyrazol-4-carbaldehyde **4a-d** with different hydrazines by using ethanol as a solvent under reflux condition with 84–94% yield.



SCHEME 1 Preparation of pyrazolcarboxaldehydes **4a-d**



SCHEME 2 Preparation of (1*H*-pyrazol-4-yl) methylene-hydrazide derivatives **5a-g** and **6a-e**

Compounds **6a-e** were synthesized from the reaction of 1*H*-pyrazol-4-carbaldehyde **4b** with hydrazine monohydrate, and aryl isothiocyanates in ethanol by using tri ethyl amine as a base catalyst at reflux condition for 5 h. The chemical structures of new pyrazole compounds **5a-g** and **6a-e** were established by analytical data (NMR, IR and HRMS). For example, the Infrared spectrum of product **5c** showed N-H absorption peak at 3214 cm^{-1} and absorption peaks at 1644, 1177 & 1129 cm^{-1} belongs to carbonyl and CF_3 groups respectively. Proton NMR of compound **5c** indicated three singlets at δ = 9.18, 8.77 and 8.61 corresponding to NH proton, HC=N proton and pyridine ring proton, one multiplet at δ = 7.43–7.70 belongs to p-fluoro aryl ring connected to pyrazole, and two doublets and one triplet at δ = 8.19, 8.32 and 7.26 due to pyridine ring protons, $\underline{C}F_3$ peak of **5c** in ^{13}C NMR spectrum appears as quartet at δ = 119.72. Moreover this was established by High Resolution Mass Spectrum information which has been showed a molecular ion peak for $C_{17}H_{11}ON_5ClF_4$ ($[M + H]^+$) at 412.0577. Further, the Infrared spectrum of the product **6a** has been showed a prominent absorption bands at 3311 and 3140 cm^{-1} due to N-H functional groups. ^1H-NMR spectrum of the compound **6a** has been showed four singlet signals at δ = 3.80, 7.86, 8.17, and 9.21 due to -OCH_3, NH, CH=N and NH protons respectively, two doublet signals at δ = 6.90 & 7.55 belongs to p-methoxy aryl ring protons, one multiplet and one triplet at δ = 7.59–7.66 & 7.32 due to p-fluorophenyl ring protons attached to pyrazole moiety, this indicate the formation of product. ^{13}C NMR spectrum of product **6a** has been showed two quartet signals at δ = 119.28 and 137.93 corresponding to $\underline{C}F_3$ and $\underline{C}$-CF_3 carbons respectively. And the mass spectrum of the product **6a** showed a molecular ion peak ($[M + H]^+$) at m/z = 472.

TABLE 1 Antibacterial activities of newly prepared products **5a-g** & **6a-e**

	Zone of inhibition (mm)					
	Gram-positive bacteria			Gram-negative bacteria		
Product	***B.l***	***B.s***	***S.a***	***E.c***	***K.p***	***P.a***
5a	06	07	09	23	18	12
5b	14	18	20	20	18	18
5c	12	07	06	19	12	07
5d	10	08	14	07	14	12
5e	14	08	12	07	16	06
5f	18	21	14	18	19	15
5 g	07	20	14	21	12	14
6a	12	19	06	07	08	06
6b	18	22	12	18	12	14
6c	14	18	18	21	18	07
6d	07	08	06	19	18	16
6e	19	23	14	12	09	08
Ciprofloxacin	24	25	25	25	24	26
Control (1% DMSO)	--	--	--	--	--	--

2.2 | Antibacterial activity

Antimicrobials constitute a significant and broad subgroup of modern drugs and is heavily dependent on in clinical treatment to treat simple infections or severe diseases. So it is fairly clear from the spectrum of use that these categories of drugs are especially significant from the medical point of view.[28] But microbial resistance caused by the over use of antimicrobials is creating a

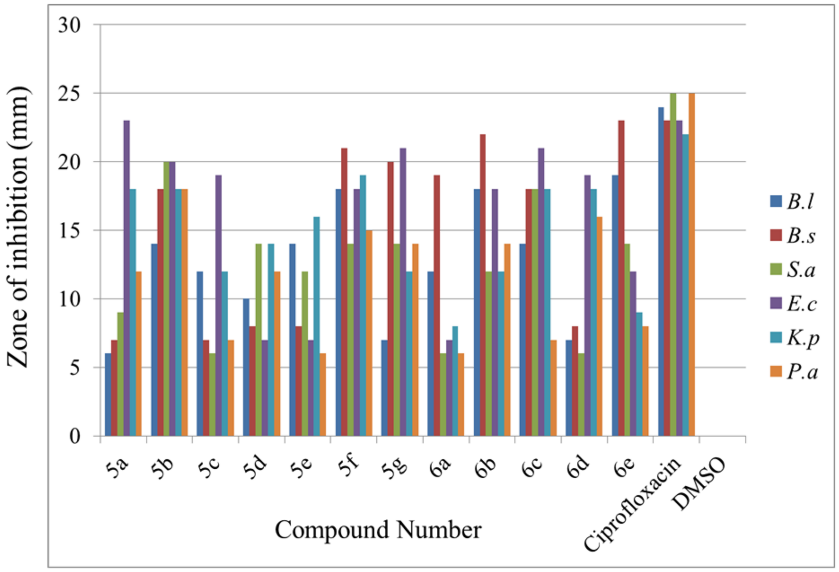


FIGURE 2 Graphical representation of antibacterial activity of prepared products **5a-g & 6a-e** [Color figure can be viewed at wileyonlinelibrary.com]

serious problem recently. Since of this development of resistance, many drugs are now useless or not efficient as before. What is more, the toxic effects produced by these antibiotics are still reducing their significance in some cases.[29] So the development of new antimicrobial is always of importance. Antibacterial activity study of newly synthesized title products **5a-g** and **6a-e** was evaluated against three Gram positive bacteria *viz.*, *Staphylococcus aureus Bacillus subtilis,* and *Bacillus licheniformis* and three Gram negative bacterial strains like *Klebsiella pneumonia, Pseudomonas aeruginosa, and Escherichia coli* using ciprofloxacin as a standard drug. The inhibition zone diameter values (mm) of the products were summarized in Table 1. From graphical representation Figure 2, inhibition zone diameter values (mm) against compounds **5a-g** and **6a-e**, possessed variable activity against tested bacterial strains as compared with standard drug. Based on the zone of inhibition produced against the tested bacteria, product **6e** was the most effective against *B. licheniformis* and *S. aureus* Gram-positive bacteria showed the maximum zone of inhibition ranging in between 19 and 23 mm, when compared with standard drug ciprofloxacin, which has been showed the maximum zone of inhibition ranging in between 24 and 25 mm against *B. licheniformis* and *S. aureus* Gram-positive bacteria. Remain products showed light activity against Gram positive and Gram negative bacteria (Table 1 and Figure 2).

TABLE 2 Antifungal activities of newly prepared products **5a-g** and **6a-e**

Compound	Zone of inhibition (mm)		
	Aspergilus Niger	*Candida albicance*	*Fusarium oxysporum*
5a	14	12	09
5b	08	06	10
5c	07	12	12
5d	12	11	12
5e	08	09	10
5f	10	14	12
5 g	12	06	07
6a	19	16	12
6b	14	12	10
6c	17	14	11
6d	06	08	12
6e	18	15	10
Nystatin	**20**	**17**	**15**
Control (1% DMSO)	--	--	--

2.3 | Antifungal activity

The antifungal activity of prepared novel pyrazole derivatives was also evaluated *in vitro* by measuring zone of inhibition values against three fungi, namely *Aspergilus niger, Candida albicance,* and *Fusarium oxysporum*. Standard antibiotic nystatin was used for relative study of antifungal activity shown by products **5a-g** and **6a**-e. Among the tested products (**5a-g** and **6a**-e) against antifungal strains revealed that the compounds **6a**, **6c** and **6e** exhibit good antifungal activity against both *Aspergilus niger* and *Candida albicance* as shown in Table 2 & Figure 3.

(–- = No activity, *B.l = Bacillus licheniformis, S.a = Staphylococcus aureus, B.s = Bacillus subtilis, E.c = Escherichia coli, K.p = Klebsiella pneumonia, P.a = Pseudomonas aeruginosa.)*

-- = No activity.

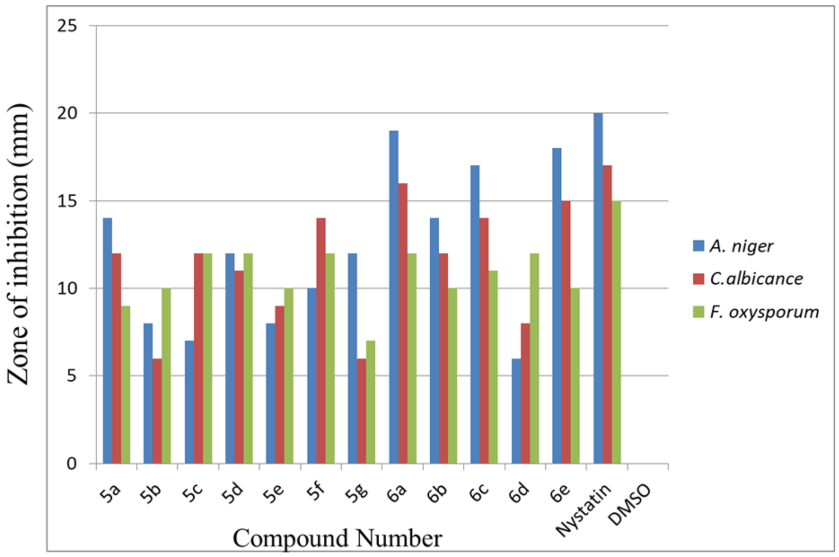


FIGURE 3 Graphical representation of antifungal activity of prepared products **5a-g & 6a-e** [Color figure can be viewed at wileyonlinelibrary.com]

3 | CONCLUSION

In conclusion we designed a simple synthesis of (1*H*-pyrazol-4-yl) methylene-hydrazide derivatives **5a**-**g** and **6a**-**e** in good yields, and tested for their antimicrobial activities. The outcome showed that the compounds **5a**-**g** & **6a**-**e** displayed unreliable inhibitory effects on the growth of the tested bacterial strains and fungal strains, with respect to reference drugs. This type of products could be used as the lead products for further structural optimization to study the significant antibacterial and antifungal activities, the research are in progress.

4 | EXPERIMENTAL SECTION

4.1 | Materials and methods

^{1}H-NMR and ^{13}C-NMR spectras were determined with Bruker AV 300 MHz and AV 75 MHz spectrometers, using $CDCl_3$ and DMSO-d_6 as a solvents and tetramethylsilane (δ) as an internal standard. Chemical shifts were given in ppm and coupling constants (*J*) were given in Hertz. All the melting points were recorded using capillarry tubes with Casiae-Siamia (VMP-AM) melting point equipment, uncorrected and reported in degrees. Infrared spectra were determined by using Perkin-Elmer FT-IR 240-C spectrophotometer with KBr disks. Mass Spectra was scanned with QSTARXL hybrid MS/MS system (Applied Biosystems. USA) under electrospray ionization. The purity of the prepared compounds was checked by precoated TLC plates, they were run on Silica Gel 60 F254 (mesh) using UV light as visualizing agent.

4.2 | Synthesis of 1*H*-pyrazol-5-ols (3a-d)

Title compounds pyrazol-5-ols **3a-d** were synthesized by using reported method.[30] Ethyl 4,4,4-trifluoro-3-oxobutanoate (50 mmol) was added to a solution of aryl hydrazine hydrochloride (55 mmol) in 20 mL of ethanol, then it was refluxed for 8 hours. The reaction mixture was cooled to room temperature, and its pH was adjusted to 7–8 with 10% sodium hydroxide solution, then 20 mL water added, again stirred the reaction mixture at room temperature for 1 hour. The resulting precipitate was filtered off, washed with chilled water, and dried under suction to obtain a solid **3**.

4.2.1 | *1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (3a)*[31]

Yield 9.8 g (86%), a light brown solid, m.p 199–201°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 5.82 (s, 1H), 7.30(t, 1H, J = 6.80 Hz), 7.38–7.51(m, 2H), 7.75(d, 2H, J = 7.55 Hz), 11.38(br, 1H, OH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 85.03, 120.51 (q, $\underline{C}F_3$, ^1J = 268.48 Hz), 121.52, 126.08, 127.97, 137.37, 140.54(q, $\underline{C}$-CF_3, ^2J = 37.41 Hz), 152.72; I. R. (ν cm^{-1}, KBr): 3424 (O-H), 1600 (C=N), 1155, 1123(CF_3); Mass (ESI^+) m/z 229 ([M + H]+).

4.2.2 | 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-ol (3b)

Yield 10.5 g (81%), a light brown solid, m.p 197–199°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 3.86 (s, 3H, -OCH_3), 5.80(s, 1H), 6.95(d, 2H, J = 8.87 Hz), 7.61(d, 2H, J = 8.87 Hz), 11.34(s, 1H, -OH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 54.32(-OCH_3), 84.42, 112.83, 120.34(q, $\underline{C}F_3$, ^1J = 270.01 Hz), 122.95, 130.18, 140.43(q, $\underline{C}$-CF_3, ^2J = 38.46 Hz), 152.09, 157.27; I. R (ν cm^{-1}, KBr): 3424 (O-H), 1565 (C=N) 1156, 1138 (CF_3); Mass (ESI^+) m/z 259 ($[M + H]^+$).

4.2.3 | *1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-ol* (3c)

Yield 10.7 g (81.5%), a cream solid, m.p 223–225°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 5.83(s, 1H), 7.41(d, 2H, J = 8.88 Hz), 7.76(d, 2H, J = 8.88 Hz), 11.48(s, 1H, -OH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 85.43, 120.69(q, $\underline{C}F_3$, ^1J = 269.03 Hz), 122.83, 128.32, 131.50, 136.41, 141.14(q, $\underline{C}$-CF_3, ^2J = 37.41 Hz), 153.22; I. R. (ν cm^{-1}, KBr): 3164 (O-H), 1593 (C=N), 1159, 1140 (CF_3); Mass (ESI^+) m/z 263 ($[M + H]^+$).

4.2.4 | *1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-ol* (3d)

Yield 10.2 g (83%), a cream solid, m.p 203–205°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 5.80 (s, 1H), 7.06–7.26(m, 2H), 7.68–7.86(m, 2H), 11.68(s, 1H, -OH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 84.83, 114.60(d, Ar-F, ^2J = 23.10 Hz), 120.34 (q, $\underline{C}F_3$, ^1J = 269.03 Hz), 123.26(d, Ar-F, ^3J = 8.25 Hz), 133.49, 140.43(q, $\underline{C}$-CF_3, ^2J = 37.96 Hz), 152.57, 160.08 (d, Ar-F, ^1J = 245.93 Hz); I. R. (ν cm^{-1}, KBr):

3419(O-H), 1601(C=N), 1179, 1138(CF_3); Mass (ESI^+) m/z 247 ($[M + H]^+$).

4.3 | Synthesis of 1*H*-pyrazole-4-carbalehydes 4a-d

The well-known 1*H*-pyrazole-4-carbaldehydes **4a-d** were synthesized from the 1*H*-pyrazole-5-ols by using Vilsmeier-Haack reaction.[32] $POCl_3$ (85 mmol) was slowly added to DMF (35 mmol) at 0 to 5°C and stirred for 30 minutes, after that 1*H*-pyrazole-5-ol (10 mmol) was added portion wise, again the mixture was stirred at 120°C for 1 hour. The reaction mixture was then cooled down to 0 to 5°C and ice was added, and the precipitated solid was filtered and dried, to afford the corresponding 1*H*-pyrazole-4-carbaldehydes.

4.3.1 | *5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde* (4a)[33]

Yield 2.1 g (77%), light yellow liquid, ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 6.79(d, 1H, J = 7.55 Hz), 6.95(t, 2H, J = 7.55 Hz), 7.19–7.28(m, 2H), 8.14(s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) = 109.57, 119.95(q, $\underline{C}F_3$, ^1J = 270.68 Hz), 125.75, 129.42, 130.13, 134.71, 136.57, 143.21(q, $\underline{C}$-CF_3, ^2J = 39.61 Hz), 184.78; Mass (ESI^+) m/z 275 ($[M + H]^+$).

4.3.2 | *5-chloro-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde* (4b)

Yield 2.67 g (88%), light brown liquid, ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 3.88(s, 3H, OCH_3), 7.04(d, 2H, J = 9.00 Hz), 7.45(d, 2H, J = 8.85 Hz), 10.04(s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) = 55.66(OCH_3), 114.58, 116.32, 120.03(q, $\underline{C}F_3$, ^1J = 270.59 Hz), 128.84, 133.90, 141.02(q, $\underline{C}$-CF_3, ^2J = 38.74 Hz), 160.77, 181.23(-CHO); Mass (ESI^+) m/z 305 ($[M + H]^+$).

4.3.3 | *5-chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde* (4c)

Yield 2.7 g (87%), light yellow syrup, ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 7.48–7.59(m, 4H), 10.07(s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) = 119.88(q, $\underline{C}F_3$, ^1J = 270.65 Hz), 116.72, 126.66, 129.74, 133.72, 134.46, 136.38, 143.04(q, $\underline{C}$-CF_3, ^2J = 39.96 Hz), 180.96; Mass (ESI^+) m/z 309 ($[M + H]^+$).

4.3.4 | *5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde* (4d)

Yield 2.4 g (82%), a cream solid, m.p 65–67°C, ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 7.21–7.30(m, 2H), 7.53–7.59(m, 2H), 10.04(s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) = 116.66(d, Ar-F, ^2J = 22.70 Hz), 119.92(q, $\underline{C}F_3$, ^1J = 270.65 Hz), 127.60(d, Ar-F, ^3J = 9.08 Hz), 132.06(d, Ar-F, ^4J = 2.27 Hz), 133.85, 142.88(q, $\underline{C}$-CF_3, ^2J = 39.96 Hz), 163.19(d, Ar-F, ^1J = 252.48 Hz), 181.03; Mass (ESI^+) m/z 293 ($[M + H]^+$).

4.4 | Synthesis of *N′*-((5-chloro-1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl) methylene)-hydrazide derivatives 5a-g

A mixture of *1H*-pyrazole-4-carbalehyde **4a-d** (1.0 mmol) and isoniazid or nicotinic acid hydrazide (1.0 mmol) in 5 mL of absolute ethanol was refluxed for 5 h. The reaction mixture solvent was removed under vacuum, and it was purified by using column packed with silica gel and n-hexane and ethyl acetate as eluents in 7:3 ratios.

4.4.1 | N′-((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)isonicotine hydrazide (5a)

Yield 0.37 g (94%), a cream solid, m.p 193–195°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 7.49–7.69(m, 5H), 7.82–7.91(m, 2H), 8.17(s, NH, 1H), 8.64 (s, 1H), 8.72–8.83(m, 2H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.52, 120.04(q, $\underline{C}F_3$, ^1J = 270.68 Hz), 121.01, 124.75, 128.68, 129.11, 133.36, 136.13, 138.05, 139.87, 148.64, 149.58, 161.56; I. R. (ν cm^{-1}, KBr): 3210(N-H), 1662(C=O), 1180, 1132(CF_3); Mass (ESI^+) m/z 416 ($[M + Na]^+$).; HRMS (ESI^+) calculated for $C_{17}H_{12}ON_5ClF_3$ ($[M + H]^+$): 394.067. Found: 394.066.

4.4.2 | N′-((5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)nicotine hydrazide (5b)

Yield 0.36 g (91%), a light brown solid, m.p 177–179°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 7.46 (t, 1H, J = 6.98 Hz), 7.50–7.63(m, 5H), 8.22(d, 1H, J = 7.55 Hz), 8.33(d, 1H, J = 7.55 Hz), 8.63(s, 1H), 8.76 (s, NH, 1H), 9.19(s, 1H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.17, 119.56(q, $\underline{C}F_3$, ^1J = 271.23 Hz), 122.31, 124.28, 128.24, 128.66, 132.61,

134.68, 135.62, 136.83, 139.44(q, C-CF_3, ^2J = 37.41 Hz), 147.67, 149.73, 151.02, 160.97; I. R. (ν cm^{-1}, KBr): 3192 (NH), 1650(C=O), 1188, 1127(CF_3); Mass (ESI^+) m/z 394 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{17}H_{12}ON_5ClF_3$ ($[M + H]^+$): 394.067. Found: 394.066.

4.4.3 | *N′-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene) nicotinehydrazide* (5c)

Yield 0.37 g (91%), a light brown solid, m.p 157–159°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 7.26 (t, 1H, J = 8.12 Hz), 7.43–7.70(m, 4H), 8.19(d, 1H, J = 7.37 Hz), 8.32(d, 1H, J = 7.18 Hz), 8.21(s, 1H), 8.37(s, 1H), 8.78(s, 1H, NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.36, 115.54(d, Ar-F, ^2J = 23.05 Hz), 119.72(q, CF_3, ^1J = 270.04 Hz), 122.82, 126.73(d, Ar-F, ^3J = 8.78 Hz), 131.96, 135.61, 137.38, 139.89(q, C-CF_3, ^2J = 38.42 Hz), 148.62, 149.27, 150.85, 161.32, 161.89(d, Ar-F, ^1J = 250.28 Hz), 166.80.; I. R. (ν cm^{-1}, KBr): 3214(N-H), 1644(C=O), 1177, 1129(CF_3); Mass (ESI^+) m/z 412 ($[M + H]^+$); HRMS (ESI^+) calculated for $C_{17}H_{11}ON_5ClF_4$ ($[M + H]^+$): 412.058. Found: 412.057.

4.4.4 | N′-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene) isonicotinohydrazide (5d)

Yield 0.38 g (92%), a light brown solid, m.p 188–190°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 7.24–7.33(m, 2H), 7.53–7.62(m, 2H), 7.86(d, 2H, J = 7.28 Hz), 8.15(s, NH, 1H), 8.64(s, 1H), 8.77(d, 2H, J = 7.28 Hz); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.32, 115.74(d, Ar-F, ^2J = 23.65 Hz), 119.93(q, CF_3, ^1J = 270.68 Hz), 121.19, 126.99(d, Ar-F, e_k; ^3J = 8.80 Hz), 128.70, 132.17, 133.64, 138.26, 141.07(q, C-CF_3, ^2J = 32.46 Hz), 149.31, 161.97, 162.28(d, Ar-F, ^1J = 250.88 Hz); I. R. (ν cm^{-1}, KBr): 3224(N-H), 1669(C=O), 1180, 1133(CF_3); Mass (ESI^+) m/z 412 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{17}H_{11}$ ON_5ClF_4 ($[M + H]^+$): 412.058. Found: 412.057.

4.4.5 | N′-((5-chloro-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene) isonicotinohydrazide (5e)

Yield 0.38 g (89%), a light brown solid, m.p 201–203°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 3.90 (s, OCH_3, 3H), 7.06(d, 2H, J = 8.87 Hz), 7.45(d, 2H, J = 8.68 Hz), 7.81–7.91(m, 2H), 8.63(s, 1H), 8.68–8.83 (m, 2H), 12.00(s, NH, 1H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 55.14, 112.35, 114.00, 120.27(q, CF_3, ^1J = 270.13 Hz), 122.91, 126.47, 129.05, 133.55, 138.05, 139.95(q, C-CF_3, ^2J = 37.61 Hz), 148.73, 149.73, 159.89, 161.42.; I. R. (ν cm^{-1}, KBr): 3223(N-H), 1666(C=O), 1176, 1122(CF_3); Mass (ESI^+) m/z 424 ($[M + H]^+$); HRMS (ESI^+) calculated for $C_{18}H_{14}N_5ClF_3O_2$ ($[M + H]^+$): 424.078. Found: 424.077.

4.4.6 | N′-((5-chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene) isonicotinohydrazide (5f)

Yield 0.40 g (93%), a light brown solid, m.p 181–183°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 7.49–7.63(m, 4H), 7.88(d, 2H, J = 7.47 Hz), 8.64(s, 1H), 8.77 (d, 2H, J = 7.92 Hz), 12.07(s, NH, 1H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.92, 120.50 (q, CF_3, ^1J = 270.68 Hz), 121.17, 126.15, 133.31, 134.74, 135.06, 137.93, 138.31, 138.90(q, C-CF_3, ^2J = 39.61 Hz), 140.03, 149.57, 161.64; I. R. (ν cm^{-1}, KBr): 3215(N-H), 1664(C=O), 1180, 1132(CF_3); Mass (ESI^+) m/z 450 ($[M + Na]^+$).; HRMS m/z calculated for $C_{17}H_{11}ON_5Cl_2F_3$ ($[M + H]^+$): 428.028. Found: 428.026.

4.4.7 | N′-((5-chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene) nicotinohydrazide (5 g)

Yield 0.39 g (92%), a light brown solid, m.p 167–169°C; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6, 300 MHz, δ ppm) = 7.45 (t, 1H, J = 7.17 Hz), 7.49–7.67(m, 4H), 8.33(d, 1H, J = 7.36 Hz), 8.62(d, 1H, J = 7.74 Hz), 8.76(s, 1H), 9.21(s, 1H), 12.05(s, NH, 1H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.43, 119.45(q, CF_3, ^1J = 270.68 Hz), 122.29, 125.67, 127.93, 128.41, 132.40, 134.30, 134.62, 136.61, 139.61(q, C-CF_3, ^2J = 39.61 Hz), 147.70, 149.93, 151.10, 161.03; I. R. (ν cm^{-1}, KBr): 3210(N-H), 1660(C=O), 1183, 1125(CF_3); Mass (ESI^+) m/z 450 ($[M + Na]^+$).; HRMS (ESI^+) calculated for $C_{17}H_{11}ON_5Cl_2F_3$ ($[M + H]^+$): 428.028. Found: 428.026.

4.5 | Preparation of 2-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl) methylene)-*N*-aryl hydrazine carbothioamide (6a-e)

A mixture of hydrazine monohydrate (1.0 mmol), aryl-isothiocyanates (1.0 mmol), and tri ethyl amine

(0.1 mmol) in 5 mL of absolute ethanol was stirred at room temperature for 10 minutes, after 10 minutes added 5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-carbaldehye **4d** (1.0 mmol), again the mixture was refluxed for 5 h. The solvent was removed under vacuum, and the residue was purified by coloumn chromatography by using n-hexane/ethyl acetate (9: 1) as eluent to get a solid product **6a-e.**

4.5.1 | 2-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-N-(4-methoxyphenyl) hydrazinecarbothioamide (6a)

Yield 0.41 g (87%), a light brown solid, m.p 174–176°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 3.80(s, 3H, OCH_3), 6.90(d, 2H, J = 8.12 Hz), 7.28–7.36(m, 2H), 7.55 (d, 2H, J = 8.30 Hz), 7.59–7.66(m, 2H), 7.86(s, 1H), 8.17 (s, 1H), 9.21(s, 1H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 53.88, 112.14, 112.27, 115.01(d, Ar-F, ^{2}J = 23.65 Hz), 119.28(q, $\underline{C}F_3$, ^{1}J = 270.13 Hz), 123.45, 126.21(d, Ar-F, ^{3}J = 8.80 Hz), 128.00, 129.27, 129.83, 131.33, 137.93(q, $\underline{C}$-CF_3, ^{2}J = 38.51 Hz), 155.63, 161.23 (d, Ar-F, ^{1}J = 249.78 Hz), 174.24; I. R. (ν cm^{-1}, KBr): 3311, 3140 (N-H), 1598 (C=N), 1193, 1141(CF_3); Mass (ESI^+) m/z 472 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{19}H_{15}N_5ClF_4OS$ ($[M + H]^+$): 472.061. Found: 472.060.

4.5.2 | N-(4-bromophenyl)-2-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl) methylene) hydrazinecarbothioamide (6b)

Yield 0.45 g (88%), a light brown solid, m.p 187–189°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 7.21–7.29(m, 2H), 7.50(d, 2H, J = 8.68 Hz), 7.53–7.59(m, 2H), 7.64(d, 2H, J = 8.87 Hz), 7.88(s, 1H, NH), 8.32(s, 1H). 9.95(s, 1H, NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.53, 115.42(d, Ar-F, ^{2}J = 23.10 Hz), 116.58, 119.71(q, $\underline{C}F_3$, ^{1}J = 270.13 Hz), 123.24, 126.48(d, Ar-F, ^{3}J = 8.80 Hz), 128.58, 130.10, 130.41, 131.68, 136.51, 138.50(q, $\underline{C}$-CF_3, ^{2}J = 39.06 Hz), 161.71(d, Ar-F, ^{1}J = 250.33 Hz), 174.19; I. R. (ν cm^{-1}, KBr): 3305, 3140(N-H), 1592(C=N), 1191, 1138(CF_3); Mass (ESI^+) m/z 520 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{18}H_{12}N_5BrClF_4S$ ($[M + H]^+$): 519.961. Found: 519.962.

4.5.3 | 2-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-N-(4-nitro phenyl) hydrazinecarbothioamide (6c)

Yield 0.40 g (84%), a yellow solid, m.p 199–201°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 7.25–7.29(m, 2H), 7.55–7.59(m, 2H), 7.85(s, 1H, NH), 8.06(d, 2H, J = 9.00 Hz), 8.28(d, 2H, J = 9.00 Hz), 9.54(s, 1H), 9.68(s, 1H, NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.83, 115.84(d, Ar-F, ^{2}J = 23.65 Hz), 120.08(q, $\underline{C}F_3$, ^{1}J = 269.58 Hz), 120.34, 123.80, 126.80 (d, Ar-F, ^{3}J = 8.80 Hz), 129.25, 131.11, 132.05, 139.03(q, $\underline{C}$-CF_3, ^{2}J = 39.61 Hz), 142.98, 143.77, 162.21(d, Ar-F, ^{1}J = 250.88 Hz), 174.20; I. R. (ν cm^{-1}, KBr): 3291, 3138 (N-H), 1566 (C=N), 1184, 1134(CF_3); Mass (ESI^+) m/z 487 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{18}H_{12}N_6ClF_4O_2S$ ($[M + H]^+$): 487.036. Found: 487.035.

4.5.4 | 2-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1 h-pyrazol-4-yl)methylene)-N-(4-fluorophenyl) hydrazinecarbothioamide (6d)

Yield 0.39 g (86%), a light brown solid, m.p 171–173°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 7.09(t, 2H, J = 8.68 Hz), 7.22–7.29(m, 2H), 7.52–7.59(m, 2H), 7.63–7.69(m, 2H), 7.87(s, 1H, NH), 9.25(s, 1H), 9.94(s, 1H, NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, δ ppm) = 112.45, 114.06(d, Ar-F, ^{2}J = 22.55 Hz), 115.31(d, Ar-F, ^{2}J = 23.65 Hz), 119.59(q, $\underline{C}F_3$, ^{1}J = 269.58 Hz), 123.88(d, Ar-F, ^{3}J = 8.25 Hz), 126.41 (d, Ar-F, ^{3}J = 9.35 Hz), 128.40, 129.89, 131.60, 133.28, 138.37(q, $\underline{C}$-CF_3, ^{2}J = 39.61 Hz), 158.66(d, Ar-F, ^{1}J = 243.18 Hz), 161.60(d, Ar-F, ^{1}J = 250.88 Hz), 174.61; I. R. (ν cm^{-1}, KBr): 3322, 3130(N-H), 1559(C=N), 1186, 1133(CF_3); Mass (ESI^+) m/z 460 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{18}H_{12}N_5ClF_5S$ ($[M + H]^+$): 460.041. Found: 460.040.

4.5.5 | 2-((5-chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-N-phenyl hydrazinecarbothioamide (6e)

Yield 0.39 g (89%), a light brown solid, m.p 177–179°C; ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) = 7.20–7.29(m, 3H), 7.40(t, 2H, J = 7.93 Hz,), 7.52–7.59(m, 2H), 7.73(d, 2H, J = 7.74 Hz), 7.90(s, 1H, NH), 9.36(s, 1H), 10.12(s, 1H, NH).; ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) = 113.08, 116.50(d, Ar-F, ^{2}J = 23.65 Hz), 120.64(q, $\underline{C}F_3$, ^{1}J = 270.13 Hz), 123.11, 125.84, 127.33(d, Ar-F,

^3J = 9.35 Hz), 128.76, 129.93, 130.30, 132.65, 137.76, 140.02(q, C-CF_3, ^2J = 39.61 Hz), 163.11(d, Ar-F, ^1J = 250.88 Hz), 175.18.; I. R. (ν cm^{-1}, KBr): 3323, 3130 (N-H), 1598 (C=N), 1200, 1137 (CF_3); Mass (ESI^+) m/z 442 ($[M + H]^+$).; HRMS (ESI^+) calculated for $C_{18}H_{13}N_5ClF_4S$ ($[M + H]^+$): 442.051. Found: 442.049.

4.6 | Antimicrobial assay

The antimicrobial activity of synthesized compounds was evaluated by the agar well diffusion method. For this study, standard sterilized filter paper disks (5 mm diameter) had been impregnated with a solution of dimethyl sulfoxide (1 mg/mL) containing the test compound, and placed in agar plate seeded with the suitable test organism in triplicate. Dimethyl sulfoxide alone was used as solvent controls. The plates were incubated for 1 to 4 days at 37°C. The anti-microbial activity was determined by measuring the diameter zone of transparent inhibition against test micro-organisms. For comparative evaluation, ciprofloxacin was used as standard antibacterial drug and nystatin was used as standard antifungal drug.[34,35]

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REFERENCES

[1] W. L. John, R. M. Patera, M. J. Plummer, B. P. Halling, D. A. Yuhas, *Pest Sci* **1994**, *42*, 29.

[2] N. Lingaiah, M. Jhansi, K. Hanmant, Gaikwad, B. Rajashaker, M. Sheeba Rani, N. J. Prameela Subhashini, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4138.

[3] E. Akbas, I. Berber, *Euro J Med Chem* **2005**, *40*, 401.

[4] S. Manfredini, R. Bazzanini, P. G. Baraldi, M. Guarneri, D. Simoni, M. E. Marongiu, A. Pani, P. L. Colla, E. Tramontano, *J. Med. Chem.* **1992**, *35*, 917.

[5] C. W. Noell, C. C. Cheng, *J. Med. Chem.* **1971**, *14*, 1245.

[6] M. Abdel-Aziz, G. A. Abuo-Rahma, A. A. Hassan, *Euro J Med Chem* **2009**, *44*, 3480.

[7] Z. Ozdemir, H. B. Kandilici, B. Gumusel, U. Calis, A. Bilgin, *Euro J Med Chem* **2007**, *42*, 373.

[8] L. Xinhua, Z. Jing, P. Chunxiu, S. Bao'an, L. Bo, *Frontiers of Chemistry in China* **2008**, *3*, 418.

[9] A. Hall, A. Billinton, S. H. Brown, N. M. Clayton, A. Chowdhury, G. M. P. Giblin, P. Goldsmith, T. G. Hayhow, D. N. Hurst, I. R. Kilford, A. Naylor, B. Passingham, L. Winyar, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3392.

[10] M. J. Genin, C. Biles, B. J. Keiser, S. M. Poppe, S. M. Swaney, W. G. Tarpley, Y. Yagi, D. L. Romero, *J. Med. Chem.* **2000**, *43*, 1034.

[11] H. Hashimoto, K. Imamura, J.-I. Haruta, K. Wakitani, *J. Med. Chem.* **2002**, *45*, 1511.

[12] A. G. Habeeb, P. N. P. Rao, E. E. Knaus, *J. Med. Chem.* **2001**, *44*, 3039.

[13] M. L. P. Price, W. L. Jorgensen, *J. am. Chem. Soc.* **2000**, *122*, 9455.

[14] R. R. Ranatunge, R. A. Earl, D. S. Garvey, D. R. Janero, L. G. Letts, A. M. Martino, M. G. Murty, S. K. Richardson, D. J. Schwalb, D. V. Young, I. S. Zemtseva, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6049.

[15] S. M. Sakya, K. M. L. DeMello, M. L. Minich, B. Rast, A. Shavnya, R. J. Rafka, D. A. Koss, H. Cheng, J. Li, B. H. Jaynes, C. B. Ziegler, D. W. Mann, C. F. Petras, S. B. Seibel, A. M. Silvia, D. M. George, L. A. Lund, S. St. Denis, A. Hickman, L. Michelle, M. L. Haven, M. P. Lynch, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 288.

[16] S. M. Sakya, H. Cheng, K. M. Lundy DeMello, A. Shavnya, M. L. Minich, B. Rast, J. Dutra, C. Li, R. J. Rafka, D. A. Koss, J. Li, B. H. Jaynes, C. B. Ziegler, D. W. Mann, C. F. Petras, S. B. Seibel, A. M. Silvia, D. M. George, A. Hickman, M. L. Haven, M. P. Lynch, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1202.

[17] T. M. Fong, S. B. Heymsfield, *Int J Obes (Lond)* **2009**, *33*, 947.

[18] S. G. Kucukguzel, S. Rollas, H. Erdeniz, M. Kiraz, A. C. Ekinci, A. Vidin, *Euro J Med Chem* **2000**, *35*, 761.

[19] M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, *J. Med. Chem.* **2000**, *43*, 953.

[20] J. Monika, B. Jagannath, Y. Samiye, E. Ayse, U. Gulberk, B. N. Sinha, S. Vadivelan, B. Arijit, J. Venkatesan, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4296.

[21] F. Rossella, D. Nicoletta, B. Mariangela, L. P. Monaco, G. Laura, Y. Matilde, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5128.

[22] C. Daniele, D. L. Alessandro, R. Marco, B. Beatrice, M. Fabrizio, M. Matteo, S. Sibilla, M. Rita, C. Lorenza, B. Maurizio, *Bioorg. Med. Chem.* **2008**, *16*, 8587.

[23] A. R. Trivedi, D. K. Dodiya, B. H. Dholariya, V. B. Kataria, V. R. Bhuva, V. H. Shah, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5181.

[24] W.-H. Lin, S.-Y. Hsieh, S.-C. Yen, C.-T. Chen, T.-K. Yeh, T. Hsu, C. T. Lu, C.-P. Chen, C.-W. Chen, L.-H. Chou, Y.-L. Huang, A.-H. Cheng, Y.-I. Chang, Y.-J. Tseng, K.-R. Yen, Y.-S. Chao, J. T.-A. Hsu, W.-T. Jiaang, *Bioorg. Med. Chem.* **2011**, *19*, 4173.

[25] S. Bhavanarushi, V. Kanakaiah, E. Yakaiah, V. Saddanapu, A. Addlagatta, *Vatsala Rani. J. Med Chem Res* **2013**, *22*, 2446.

[26] S. Bhavanarushi, V. Kanakaiah, G. Bharath, A. Gangagnirao, *Vatsala Rani. J. Med Chem Res* **2014**, *23*, 158.

[27] S. Bhavanarushi, G. Bharath, A. Gangagnirao, J. Vatsala Rani, *J. Heterocyclic Chem.* **2016**, *53*, 754.

[28] J. Salimon, N. Salih, H. Hussien, *Eur. J. Sci. Res.* **2009**, *31*, 256.

[29] J. Salimon, N. Salih, E. J. Yousif, *King Saud Univ. (Science)* **2011**, *23*, 399.

[30] (a) L. Mei, X. Zhili, E. Clampit Jill, W. Sanyi, J. Gum Rebecca, L. Haasch Deanna, M. Trevillyan James, A.-Z. Cele, H. Fry Elizabeth, L. Sham Hing, L. Gang, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2590; (b) M. A. Khan, G. P. Ellis, *M. c., J Heterocycl Chem* **2001**, *38*, 193; (c) K. Reiner, R. Richter, S. Hauptmann, J. Becher, L. Hennig, *Tetrahedron* **1995**, *51*, 13291.

[31] Uchida Yukio.; Atsuminaoya. Euopean patent EP1990336A1, 2008.

[32] (a) W. Holzer, K. Hahn, *J Heterocycl Chem* **2003**, *40*, 303; (b) F. M. Abd El Latiff, *J Heterocycl Chem* **2000**, *37*, 1659.

[33] Takahashi Satoru.; Ueno Ryohei.; Yamaji Yoshihiro.; Fujinami Makoto. US patent US2005/256004A1, **2005**.

[34] M. A. Patel, V. G. Bhila, N. H. Patel, A. K. Patel, D. I. Brahmbhatt, *Med. Chem. Res.* **2012**, *21*, 4381.

[35] A. P. Keche, G. D. Hatnapure, R. T. Tale, A. H. Rodge, S. S. Birajdar, V. M. Kamble, *Med. Chem. Res.* **2013**, *22*, 1480.

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