Synthesis of Isoxazole, 1, 2, 4-Oxadiazole and (1*H*-Pyrazol-4-yl)-methanone Oxime Derivatives from *N*-Hydroxy-1*H*-pyrazole-4-carbimidoyl Chloride and their Biological Activity

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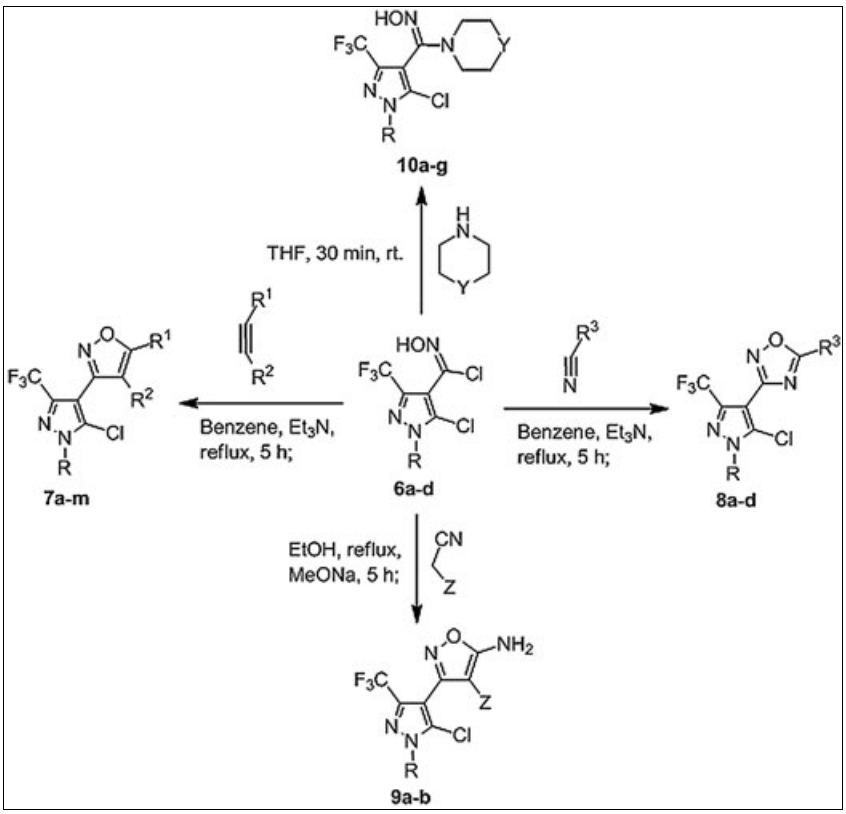

Some novel isoxazole-, 1,2,4 oxadiazole-, and (1*H*-pyrazol-4-yl)-methanone oxime derivatives were synthesized from *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chloride and the structures of all products were identified by spectral data (^{1}H-NMR, ^{13}C-NMR, IR, MS, and HRMS) and evaluated their antibacterial activity.

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INTRODUCTION

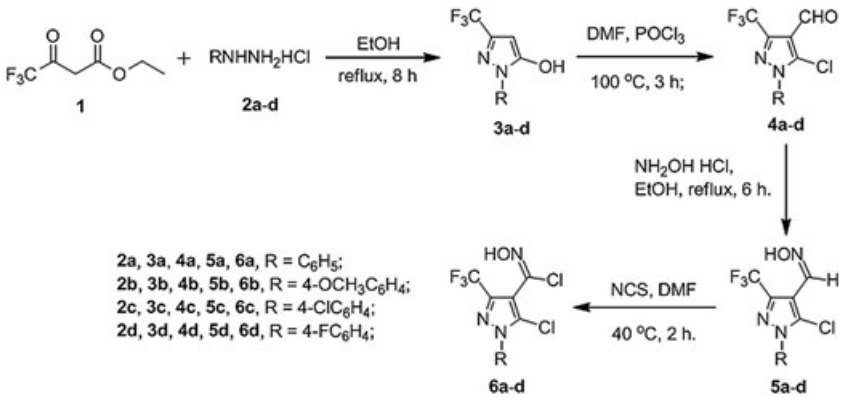
Heterocyclic compounds with pyrazole moiety were found to be valuable intermediates for medicinal drugs [1]. They have wide-ranging collection of conventional biological and pharmaceutical activities, such as antitumor [2,3], anti-inflammatory, analgesic, antipyretic [4], antiviral [5], antimicrobial [6,7], anti-ischemic effects [8], sodium channel blocker [9], hypoglycaemic [10,11], anti-hypertensive [12], antiangiogenic [13], antioxidant [14], antidepressant, anxiolytic, neuroprotective [15], and antidiabetic [16] activity. Pyrazole nucleus containing drugs are widely used in the treatment of ulcerative colitis, inflammatory bowel syndrome [17], atherosclerosis [18], and Alzheimer's disease [19]. Heterocyclic rings and, in particular, the pyrazole ring, represent an expedient choice for the synthesis of pharmaceutical compounds with different activities and noble safety profiles [20]. In continuation of our research work on synthesis of trifluoromethyl substituted pyrazole derived heterocycles [21,22] and due to the wide applications of pyrazole derivatives in medicinal chemistry, we wish to synthesize various heterocyclic compounds containing pyrazole as a core moiety and screening of their antibacterial activity.

RESULTS AND DISCUSSION

We synthesized the compounds **6a–d** by known procedure [23,24], which involves the reaction of ethyl-trifluoroacetoacetate **1** with hydrazine hydrochlorides **2a–d**, in ethanol yielded the corresponding 3-(trifluoromethyl)-1*H*-pyrazol-5-ol **3a–d**. Treatment of 1*H*-pyrazol-5-ol **3a–d**, with $POCl_3$ in dimethylformamide (DMF) led to the formation of corresponding 5-chloro-1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-4-carbaldehyde **4a–d**. The reaction of 4-formylpyrazole **4a–d** with hydroxylamine hydrochloride in EtOH gave the corresponding pyrazole oximes **5a–d** in good yield, which on reaction with NCS in DMF affords *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chloride **6a–d** as shown in Scheme 1.

In medicinal chemistry, chloro oxime derivatives constitute a class of compounds that have served as useful intermediates towards construction of various heterocyclic compounds such as isoxazoles [25], oxadiazoles [26], benzimidazoles, benzothiazoles, and benzoxazoles [27]. By using this chloro oxime derivatives **6a–d**, we synthesized novel isoxazoles (**7a–m** and **9a–b**) and oxadiazoles (**8a–d**) as shown in Scheme 2. The compounds (1*H*-pyrazol-4-yl)-isoxazole **7a–m** were obtained by cyclization of *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chloride **6a–d** with alkynes in the presence of Et_3N by using benzene as a solvent. The compounds **7a–m** along with their yields is given in Table 1. The structures of compounds **7a–m** were confirmed by their spectroscopic data (^{1}H-NMR, ^{13}C-NMR, and MS) and data provided in the experimental section. The ^{1}H-NMR of compound **7b** showed a singlet signal at $\delta = 3.87$ corresponding to methoxy protons, singlet at $\delta = 6.70$ corresponding to –CH proton, the two doublets at $\delta = 7.01$ and 7.80 corresponding to p-methoxy phenyl ring protons attached to isoxazole ring and multiplet at

Scheme 1. Preparations of compounds **6a–d**.



Scheme 2. Preparation of compounds **7a–m**, **8a–d**, and **9a–b**.

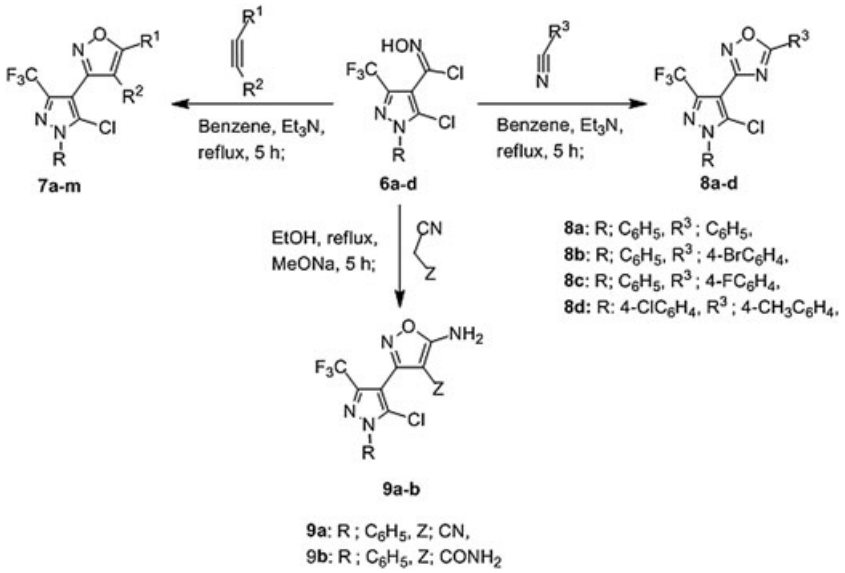


Table 1

Compounds **7a–m** along their yields.

Entry	R	R^1	R^2	Product	Time (h)	Yield[a] (%)
1	C_6H_5	C_6H_5	H	**7a**	5	80
2	C_6H_5	4-$OCH_3C_6H_4$	H	**7b**	5	78
3	C_6H_5	4-$NO_2C_6H_4$	H	**7c**	5	77
4	C_6H_5	4-BrC_6H_4	H	**7d**	5	76
5	C_6H_5	4-FC_6H_4	H	**7e**	5	73
6	C_6H_5	C_6H_5	C_6H_5	**7f**	5	48
7	C_6H_5	CO_2Et	CO_2Et	**7 g**	5	67
8	4-FC_6H_4	C_6H_5	H	**7 h**	5	70
9	4-FC_6H_4	4-$OCH_3C_6H_4$	H	**7i**	5	67
10	4-FC_6H_4	4-$NO_2C_6H_4$	H	**7j**	5	61
11	4-FC_6H_4	4-FC_6H_4	H	**7 k**	5	69
12	4-$OCH_3C_6H_4$	C_6H_5	H	**7 l**	5	65
13	4-$OCH_3C_6H_4$	4-$NO_2C_6H_4$	H	**7 m**	5	62

[a]Isolated yield

$\delta = 7.52–7.63$ corresponding to phenyl group protons attached to pyrazole moiety. It was also confirmed by high-resolution mass spectrometry (HRMS) data which shows peak for $C_{20}H_{14}O_2N_3ClF_3$ $(M + H^+)$ at 420.0702. The compounds (1*H*-pyrazol-4-yl)-oxadiazole **8a–d** were obtained by cyclization of *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chloride **6a** and **6c** with aromatic nitriles in the presence of Et_3N using benzene as a solvent. The structures of compounds **8a–d** were confirmed by their spectroscopic data (^{1}H-NMR, ^{13}C-NMR, and MS) and data provided in the experimental section. The ^{1}H-NMR of compound **8a** shows two multiplets at $\delta = 7.54–7.64$ and 8.20–8.23 corresponding to two phenyl group protons attached to pyrazole and oxadiazol rings, and it was also confirmed by HRMS data which shows peak for $C_{18}H_{11}ON_4ClF_3$ $(M + H^+)$ at 391.0571. On the other hand, when *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chloride **6a** was reacted with malononitrile and cyanoacetamide afford isoxazole derivatives **9a** and **b** in moderate yield (63–68%). The structures of compounds **9a** and **b** were confirmed by their spectroscopic data (^{1}H-NMR, ^{13}C-NMR, and MS) and data provided in the experimental section. The ^{1}H-NMR of compound **9a** shows multiplet at $\delta = 7.44–7.63$ corresponding to phenyl group protons attached to pyrazole ring, and broad singlet at $\delta = 8.00$ corresponding to NH_2 protons. The infrared spectrum of compound **9a** shows characteristic absorptions corresponding to NH_2 (3367 and 3211 cm^{-1}) and CN (2234 cm^{-1}) groups, and it was also confirmed by HRMS data which shows peak for $C_{14}H_8ON_5ClF_3$ $(M + H^+)$ at 354.0363.

We also synthesized (1*H*-pyrazol-4-yl)methanone oximes from chloro oxime (**6a** and **c**), which were reacted with cyclic secondary amines such as morpholine, piperidine, 4-phenylpiperazin, 4-benzylpiperdine, to obtain the corresponding (1*H*-pyrazol-4-yl)methanone oximes **10a–g** as shown in Scheme 3 and the results are shown in Table 2.

Scheme 3. Synthesis of (1*H*-pyrazol-4yl)methanone oximes **10a–g**.

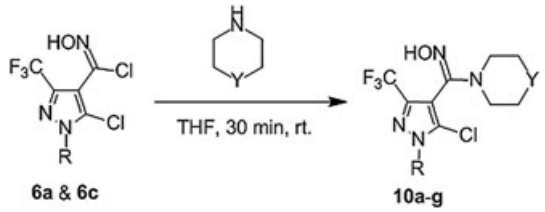


Table 2

Compounds **10a–g** along their yields.

Entry	R	Y	Product	Time (min)	Yield[a] (%)
1	C_6H_5	CH_2	**10a**	15	59
2	C_6H_5	O	**10b**	15	70
3	C_6H_5	CH-CH_2-C_6H_5	**10c**	15	65
4	C_6H_5	N-C_6H_5	**10d**	15	67
5	4-ClC_6H_4	CH_2	**10e**	15	62
6	4-ClC_6H_4	CH-CH_2-C_6H_5	**10f**	15	64
7	4-ClC_6H_4	N-C_6H_5	**10 g**	15	69

[a]Isolated yield

The structures of compounds **10a–g** were confirmed by their spectroscopic data (^{1}H-NMR, ^{13}C-NMR, and MS) and data provided in the experimental section. The ^{1}H-NMR spectrum of compound **10e** shows two multiplets at $\delta = 1.42–1.68$ and 2.97–3.21, corresponding to piperidine ring, protons one broad singlet at $\delta = 7.20$ corresponding to oxime proton, and protons one multiplet at $\delta = 7.38–7.62$ corresponding to 4-chlrophenyl group protons attached to pyrazole ring. The IR spectrum of compound **10e** shows characteristic absorption bands at 3285 cm^{-1} (N–OH), 1624 cm^{-1} (C=N), and it was also confirmed by HRMS data which shows peak for $C_{16}H_{16}ON_4Cl_2F_3$ $(M + H^+)$ at 407.0631.

Table 3

Antibacterial activity of newly synthesized compounds.

	Zone of inhibition (mm)					
	Gram-negative (−ve) bacteria			Gram positive (+ve) bacteria		
Organic compound	*Escherichia coli*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Bacillus licheniformis*	*Bacillus subtilis*	*Staphylococcus aureus*
7a	—	—	—	—	—	—
7b	—	—	—	—	—	—
7c	—	—	—	—	—	—
7d	—	—	—	—	—	
7e	—	—	—	—	—	—
7f	—	—	—	—	—	—
7g	—	—	—	—	—	—
7h	—	—	—	—	—	—
7i	—	—	—	—	—	—
7j	—	—	—	—	—	—
7k	—	—	—	—	—	—
7l	—	—	—	—	—	—
7m	—	—	—	—	—	—
8a						
8b	—	—	—	—	—	—
8c	—	—	—	—	—	—
8d	—	—	—	—	—	—
9a	20	19	21	19	19	19
9b	—	—	—	—	—	—
10a	—	—	—	—	—	—
10b	—	—	—	—	—	—
10c	—	—	—	—	—	—
10d	—	—	—	—	—	—
10e	—	—	—	—	—	—
10f	—	—	—	—	—	—
10g	—	—	—	—	—	—
Cloxacillin	—	—	—	—	—	21
Ciprofloxacin	26	24	25	24	23	25
Control (1% DMSO)	—	—	—	—	—	—

—, no activity.

Antibacterial evaluation. The 26 newly synthesized target compounds were evaluated for their antibacterial activity against three Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumonia, Pseudomonas aeruginosa,* and three gram positive bacteria like *Bacillus licheniformis, Bacillus subtilis,* and *Staphylococcus aureus.* Agar diffusion method was used for the determination of the preliminary antibacterial activity. Ciprofloxacin and cloxicilin were used as reference drugs. The results were recorded for each tested compound diameter of inhibition zones of microbial growth around the disks in mm. The inhibition zone diameters values are revealed in Table 3. The compound **9a** shows good activities against (inhibitory zone ≥ 20 mm) bacterial strains.

CONCLUSION

In conclusion, we have described synthesis of novel trifluoromethyl substituted pyrazole derived heterocycles such as isoxazoles, oxadiazoles, and (1*H*-pyrazol-4-yl)-methanone oxime derivatives from *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chlorides and evaluated for their antibacterial activity.

EXPERIMENTAL

General. Melting points were determined on a Casiae-Siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 240-C spectrophotometer using KBr optics. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AV 300 MHz in $CDCl_3$ (or DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ ppm and coupling constants (*J*) are given in Hz. Electron Spray ionization (ESI) and high-resolution mass spectra were recorded on a QSTARXL hybrid MS/MS system (Applied Bio systems, USA) under electrospray ionization. Thin-layer chromatography was performed on pre-coated silica gel 60 F254 (mesh); spots were visualized with ultraviolet light.

Preparation of 5-pyrazolones 3a–d. The compounds **3a–d** was prepared using reported procedure [28] with minor modifications. To a stirred solution of hydrazine hydrochloride (0.1 mol) and absolute ethanol (10 mL), the solution of ethyltrifluoroacetoacetate (0.1 mol) with absolute ethanol

(10 mL) was added at 25–30°C, and the mixture was refluxed for 8 h. Then cooled to room temperature, adjusted the pH value of mixture to 7 using 10% NaOH solution, added 20 mL water, and stirred for 1 h at room temperature. The precipitated solid was filtered and washed with cold water to get a solid.

Preparation of 5-chloro-4-formylpyrazoles 4a–d. The known 5-chloro-4-formylpyrazoles were prepared from the 5-pyrazolones employing Vilsmeier-Haack chloro formylation [29]. Thus, 5-pyrazolones were heated with an excess phosphorus oxychloride in DMF to afford the corresponding 5-chloro-4-formyl pyrazoles **4a–d**.

Preparation of pyrazole oximes 5a–d. The treatment of 4-formyl pyrazole **4a–d** (1.0 mmol) with hydroxyl amine hydrochloride (1.5 mmol) in EtOH (5 mL) reflux for 5 hours gave the corresponding pyrazole oximes **5a–d** in good yield. All pyrazole oximes purified by a column with silica gel using petroleum ether/ethyl acetate (8.5:1.5 v/v) mixture to obtain pure products of **5a–d**.

Preparation of N-hydroxy-1H-pyrazole-4-carbimidoyl chloride 6a–d. The reaction of pyrazole oxime **5a–d** (1.0 mmol) with NCS (1.5 mmol) in DMF (2 mL) at 40°C for 2 h gave the corresponding *N*-hydroxy-1*H*-pyrazole-4-carbimidoyl chlorides **6a–d**.

General procedure for the synthesis of compounds 7a–m or 8a–d. The alkyne or nitrile (1.0 mmol) and *N*-hydroxy-pyrazole-carboximidoyl chloride (1.0 mmol) were dissolved in benzene (5 mL). A solution of triethylamine (1.0 mmol) in benzene (2 mL) was added dropwise to the aforementioned mixture and refluxed for 5 h. Then the triethylamine hydrochloride was filtered off, the solvent removed in vacuo, and the residue purified by a column with silica gel using petroleum ether/ethyl acetate (9.5:0.5 v/v) mixture to obtain pure products of **7a–m** or **8a–d**.

3-(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-phenyl isoxazole (7a). Cream solid; yield: 0.31 g (80%); mp 142–144°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.34 (d, J = 7.93 Hz, 1H), 6.84 (s, 1H, CH), 6.98 (t, J = 7.18 Hz, 1H), 7.07 (d, J = 8.31 Hz, 2H), 7.39 (t, J = 6.99 Hz, 2H), 7.52–7.65 (m, 3H), 8.05 (d, J = 7.74 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 99.65, 108.25, 120.47 (q, ^1J = 270.65 Hz, CF_3), 125.52, 125.89, 126.90, 129.04, 129.36, 129.41, 129.78, 130.52, 137.00, 140.85 (q, ^2J = 38.14 Hz, CF_3), 153.16, 170.56; MS (ESI), *m/z*: 390 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{12}ON_3ClF_3$ ($M+H^+$), 390.0615; found, 390.0610.

3-(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-methoxyphenyl)isoxazole (7b). Light brown solid; yield: 0.32 g (78%); mp 143–145°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.87 (s, 3H, OCH_3), 6.70 (s, 1H, CH), 7.01 (d, J = 8.69 Hz, 2H), 7.52–7.63 (m, 5H), 7.80 (d, J = 8.69 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 55.38 (OCH_3), 98.31, 114.44, 120.50 (q, ^1J = 270.65 Hz, CF_3), 119.75, 125.53, 127.12, 127.52, 128.63, 129.34, 129.75, 137.05, 140.86 (q, ^2J = 38.14 Hz, CF_3), 153.10, 161.33, 170.54; MS (ESI), *m/z*: 420 ($M+H^+$); HRMS *m/z* calcd for $C_{20}H_{14}O_2N_3ClF_3$ ($M+H^+$), 420.0721; found, 420.0702.

3-(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-nitro phenyl)isoxazole (7c). Cream solid; yield: 0.33 g (77%); mp 172–174°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.01 (s, 1H, CH), 7.27 (t, J = 8.31 Hz, 3H), 7.57–7.63 (m, 2H), 8.04 (d, J = 8.88 Hz, 2H), 8.38 (d, J = 8.69 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 102.15, 107.54, 120.35 (q, ^1J = 269.74 Hz, CF_3), 124.37, 125.42, 126.68, 129.35, 129.55, 129.85, 132.20, 136.81, 140.74 (q, ^2J = 38.14 Hz, CF_3), 148.56, 153.54, 167.91; MS (ESI), *m/z*: 435 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{11}O_3N_4ClF_3$ ($M+H^+$), 435.0466; found, 435.0461.

5-(4-Bromophenyl)-3-(5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)isoxazole (7d). White solid; yield: 0.35 g (76%); mp 139–141°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.83 (s, 1H, CH), 7.54–7.62 (m, 5H), 7.65 (d, J = 8.55 Hz, 2H), 7.73 (d, J = 8.55 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 100.02, 108.04, 120.46 (q, ^1J = 269.74 Hz, CF_3), 124.95, 125.52, 125.81, 127.34, 129.38, 129.46, 129.83, 132.35, 136.99, 140.85 (q, ^2J = 39.05 Hz, CF_3), 153.32, 169.49; MS (ESI), *m/z*: 470 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{11}BrClF_3N_3O$ ($M+H^+$), 467.9721; found, 467.9716.

3-(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-fluorophenyl)isoxazole (7e). Light brown solid; yield: 0.30 g (73%); mp 119–121°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.78 (s, 1H, CH), 7.20 (t, J = 8.69 Hz, 2H), 7.52–7.63 (m, 5H), 7.82–7.89 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 99.45, 108.13, 116.30 (d, ^2J = 22.70 Hz, Ar-F), 120.47 (q, ^1J = 270.65 Hz, CF_3), 123.31 (d, ^4J = 2.72 Hz, Ar-F), 125.51, 128.02 (d, ^3J = 8.17 Hz, Ar-F), 129.36, 129.43, 129.80, 137.00, 140.84 (q, ^2J = 38.14 Hz, CF_3), 153.26, 163.92 (d, ^1J = 251.58 Hz, Ar-F), 169.59; MS (ESI), *m/z*: 408 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{11}ON_3ClF_4$ 408.0521; found, 408.0509.

3-(5-Chloro-1-Phenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-4,5-diphenyl isoxazole (7f). Cream solid; yield: 0.22 g (48%); mp 109–111°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.19–7.25 (m, 2H), 7.30–7.41 (m, 5H), 7.43–7.58 (m, 6H), 7.60–7.65 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 99.40, 108.97, 120.10 (q, ^1J = 270.65 Hz, CF_3), 125.20, 126.92, 128.32, 128.73, 128.87, 129.25, 129.60, 129.69, 130.14, 136.47, 136.95, 139.40 (q, ^2J = 39.05 Hz, CF_3), 153.57, 169.66; MS (ESI), *m/z*: 466 ($M+H^+$); HRMS *m/z* calcd for $C_{25}H_{16}ON_3ClF_3$ ($M+H^+$), 466.0928; found, 466.0923.

Diethyl-3-(5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)isoxazole-4,5-dicarboxylate (7g). Brown liquid; yield: 0.30 g (67%); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, J = 7.17 Hz, 3H), 1.46 (t, J = 7.17 Hz, 3H), 4.30 (q, J = 7.17 Hz, 2H), 4.52 (q, J = 7.17 Hz, 2H), 7.53–7.58 (m, 3H), 7.60 (d, J = 7.47 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 13.71 (CH_3), 13.93 (CH_3), 61.99 (CH_2), 63.25 (CH_2), 106.07, 115.68, 120.08 (q, ^1J = 270.65 Hz, CF_3), 125.26, 129.36, 129.81, 130.06, 136.86, 141.76 (q, ^2J = 39.05 Hz, CF_3), 152.72, 156.00, 159.19 (C=O), 161.69 (C=O); IR (KBr, cm^{-1}): 2984, 2933 (CH), 1737 (CO), 1595 (C=N), 1182, 1143 (C-F); MS (ESI), *m/z*: 458 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{16}O_5N_3ClF_3$ ($M+H^+$), 458.0725; found, 458.0700.

3-(5-Chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-phenylisoxazole (7h). Light brown solid; yield: 0.28 g (70%); mp 111–113°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.82 (s, 1H, CH), 7.20–7.30 (m, 2H), 7.46–7.54 (m, 3H), 7.56–7.63 (m, 2H), 7.83–7.89 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 99.60, 108.33, 116.45 (d, ^2J = 23.61 Hz, Ar-F), 120.42 (q, ^1J = 270.65 Hz, CF_3), 125.89, 126.86, 127.60 (d, ^3J = 9.08 Hz, Ar-F), 129.05, 129.57, 130.56, 133.02, 140.95 (q, ^2J = 38.14 Hz, CF_3), 153.04, 162.93 (d, ^1J = 250.67 Hz, Ar-F), 170.63; MS (ESI), *m/z*: 408 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{11}ON_3ClF_4$ ($M+H^+$), 408.0521; found, 408.0509.

3-(5-Chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-methoxyphenyl) isoxazole (7i). Light brown solid; yield: 0.24 g (57%); mp 127–129°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 3H, OCH_3), 6.69 (s, 1H, CH), 7.01 (d, J = 8.55 Hz, 2H),

7.22–7.28 (m, 2H), 7.56–7.61 (m, 2H), 7.79 (d, J = 8.55 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 55.37, 98.26, 108.48, 114.45, 116.41 (d, ^2J = 23.10 Hz, Ar-F), 120.34 (q, ^1J = 271.23 Hz, CF_3), 119.67, 127.58 (d, ^3J = 9.90 Hz, Ar-F), 129.50, 133.04, 140.95 (q, ^2J = 38.51 Hz, CF_3), 152.95, 162.94 (d, ^1J = 250.88 Hz, Ar-F), 161.36, 170.61; MS (ESI), *m/z*: 438 ($M+H^+$); HRMS *m/z* calcd for $C_{20}H_{13}O_2N_3ClF_4$ ($M+H^+$), 438.0626; found, 438.0615.

3-(5-Chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-nitrophenyl) isoxazole (7j). White solid; yield: 0.26 g (51%); mp 134–136°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.01 (s, 1H), 7.23–7.30 (m, 2H), 7.57–7.64 (m, 2H), 8.04 (d, J = 8.88 Hz, 2H), 8.38 (d, J = 8.69 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 102.13, 107.72, 116.54 (d, ^2J = 23.61 Hz, Ar-F), 120.34 (q, ^1J = 270.65 Hz, CF_3), 124.48, 126.74, 127.60 (d, ^3J = 8.17 Hz, Ar-F), 129.76, 132.23, 132.93, 140.45 (q, ^2J = 39.05 Hz, CF_3), 148.69, 153.51, 163.05 (d, ^1J = 250.67 Hz, Ar-F), 168.07; MS (ESI), *m/z*: 453 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{10}ClF_4N_4O_3$ ($M+H^+$), 453.0372; found, 453.0368.

3-(5-Chloro-1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-fluorophenyl) isoxazole (7k). Light brown solid; yield: 0.21 g (52%); mp 119–121°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.76 (s, 1H), 7.20 (t, J = 8.54 Hz, 2H), 7.25 (t, J = 8.54 Hz, 2H), 7.57–7.61 (m, 2H), 7.83–7.87 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 99.44, 108.28, 116.23 (d, ^2J = 9.90 Hz, Ar-F), 116.53 (d, ^2J = 11.00 Hz, Ar-F), 120.50 (q, ^2J = 270.13 Hz, CF_3), 123.35, 127.59 (d, ^3J = 8.80 Hz, Ar-F), 128.04 (d, ^3J = 8.25 Hz, Ar-F), 129.57, 133.10, 138.82 (q, ^2J = 39.42 Hz, CF_3), 153.15, 163.01 (d, ^1J = 250.32 Hz, Ar-F), 163.98 (d, ^1J = 251.98 Hz, Ar-F), 169.68; MS (ESI), *m/z*: 426 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{10}ON_3ClF_5$ ($M+H^+$), 426.0427; found, 426.0414.

3-(5-Chloro-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-phenylisoxazole (7l). Light brown solid; yield: 0.27 g (65%); mp 113–115°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, OCH_3, 3H), 6.82 (s, 1H), 7.04 (d, J = 8.69 Hz, 2H), 7.47–7.53 (m, 5H), 7.86 (d, J = 6.86 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 55.56, 99.65, 114.44, 114.67, 119.78, 120.55 (q, ^1J = 270.65 Hz, CF_3), 125.90, 126.19, 126.60, 127.03, 129.05, 129.89, 130.51, 137.05, 141.32 (q, ^2J = 38.14 Hz, CF_3), 160.46, 170.51; MS (ESI), *m/z*: 420 ($M+H^+$); HRMS *m/z* calcd for $C_{20}H_{14}O_2N_3ClF_3$ ($M+H^+$), 420.0721; found, 420.0702.

3-(5-Chloro-1-(4-methoxyhenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-nitrophenyl) isoxazole (7m). Cream solid; yield: 0.28 g (62%); mp 141–143°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, OCH_3, 3H), 7.00 (s, 1H), 7.02 (d, J = 8.85 Hz, 2H), 7.05 (d, J = 9.00 Hz, 2H), 7.44 (d, J = 9.00 Hz, 2H), 7.50 (d, J = 8.85 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 55.13, 101.12, 109.91, 113.97, 119.96 (q, ^1J = 270.66 Hz, CF_3), 125.48, 126.39, 126.84, 129.30, 129.61, 133.89, 139.88 (q, ^2J = 37.23 Hz, CF_3), 148.43, 154.52, 159.92, 166.07; MS (ESI), *m/z*: 465 ($M+H^+$); HRMS *m/z* calcd for $C_{20}H_{12}ClF_3N_4O_4$ ($M+H^+$) 465.0572; found, 465.0568.

3-(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-phenyl-1,2,4-oxadizole (8a). White solid; yield: 0.22 g (58%); mp 117–119°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.54–7.64 (m, 8H), 8.20–8.23 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 106.60, 119.99 (q, ^1J = 270.59 Hz, CF_3), 123.75, 125.55, 128.21, 129.13, 129.37, 129.88, 130.20, 133.04, 136.84, 141.52 (q, ^2J = 38.97 Hz, CF_3), 161.00, 175.90; MS (ESI), *m/z*: 391 ($M+H^+$); HRMS *m/z* calcd for $C_{18}H_{11}ON_4ClF_3$ ($M+H^+$) 391.0568; found, 391.0571.

5-(4-Bromophenyl)-3-(5-chloro-1-Phenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-oxadiazole (8b). Light brown solid; yield: 0.24 g (53%); mp 143–145°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.53–7.62 (m, 5H), 7.72 (d, J = 8.55 Hz, 2H), 8.08 (d, J = 8.55 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 108.60, 120.54 (q, ^1J = 270.04 Hz, CF_3), 122.65, 125.56, 128.12, 129.40, 129.60, 129.92, 132.57, 136.81, 139.46 (q, ^2J = 39.34 Hz, CF_3), 143.97, 161.13, 175.10; MS (ESI), *m/z*: 471 ($M+H^+$); HRMS *m/z* calcd for $C_{18}H_{10}BrClF_3N_4O(M+H^+)$, 468.9673; found, 468.9668.

3-(5-Chloro-1-Phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(4-fluorophenyl)-1,2,4-oxadiazole (8c). White solid; yield: 0.22 g (56%); mp 125–127°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.17 (t, J = 8.69 Hz, 2H), 7.25 (t, J = 8.69 Hz, 1H), 7.53–7.63 (m, 3H), 7.65–7.72 (m, 2H), 8.20–8.27 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 108.37, 116.71 (d, ^2J = 22.50 Hz, Ar-F), 117.90, 120.09 (q, ^1J = 270.04 Hz, CF_3), 125.45, 129.03, 129.30, 129.83, 130.62 (d, ^3J = 8.78 Hz, Ar-F), 136.73, 139.41 (q, ^2J = 39.42 Hz, CF_3), 160.94, 165.01 (d, ^1J = 254.67 Hz, Ar-F), 174.86; MS (ESI), *m/z*: 431 ($M+Na^+$); HRMS *m/z* calcd for $C_{18}H_{10}ON_4ClF_4$ ($M+H^+$), 409.0473; found, 409.0467.

3-(5-Chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-5-(p-tolyl)-1,2,4-oxadiazole (8d). White solid; yield: 0.23 g (54%); mp 189–191°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.46 (s, 3H, CH_3), 7.36 (d, J = 8.09 Hz, 2H), 7.53–7.59 (m, 4H), 8.10 (d, J = 8.09 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 21.77, 107.01,121.02, 120.06 (q, ^1J = 270.65 Hz, CF_3), 126.78, 128.22, 129.63, 130.69, 135.34, 135.97, 141.87 (q, ^2J = 39.05 Hz, CF_3), 143.95, 160.75, 176.13; MS (ESI), *m/z*: 439 ($M+H^+$); HRMS *m/z* calcd for $C_{19}H_{12}ON_4Cl_2F_3$ ($M+H^+$), 439.0334; found, 439.0329.

General procedure for the synthesis of compounds 9a and b. The *N*-hydroxy-pyrazole-carboximidoyl chloride (1.0 mmol), malononitrile/cyanoacetamide (1.0 mmol), and sodium methoxide(1.0 mmol) were dissolved in ethanol (15 mL), refluxed for 5 h. After completion of the reaction, the residue was filtered off, solvent removed in vacuo, and the residue purified by a column with silica gel using petroleum ether/ethyl acetate (8:2 v/v) mixture to obtain pure products of **9a** and **b**.

5-Amino-3-(5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)isoxazole-4-carbonitrile (9a). Light brown solid; yield: 0.24 g (68%); mp 193–195°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.44–7.63 (m, 5H), 8.00 (br, 2H, NH_2); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 100.04, 105.67, 111.98, 119.59 (q, ^1J = 270.13 Hz, CF_3), 124.84, 128.88, 129.39, 129.59, 136.27, 141.09 (q, ^2J = 37.41 Hz, CF_3), 152.67, 173.04; IR (KBr, cm^{-1}): 3367, 3211 (NH_2), 2234 (CN), 1190, 1138 (C-F); MS (ESI), *m/z*: 354 ($M+H^+$); HRMS *m/z* calcd for $C_{14}H_8ON_5ClF_3$ ($M+H^+$), 354.0364; found, 354.0363.

5-Amino-3-(5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)isoxazole-4-carboxamide (9b). Light brown solid; yield: 0.23 g (63%); mp 197–199°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.78 (s, NH_2, 2H), 7.43 (br, CO-NH_2, 2H), 7.57 (d, J = 7.36 Hz, 2H), 7.61–7.66 (m, 3H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 87.85, 106.70, 119.71 (q, ^1J = 270.68 Hz, CF_3), 124.89, 125.19, 129.01, 129.39, 129.54, 136.43, 139.57 (q, ^2J = 32.46 Hz, CF_3), 149.25, 164.02, 172.31; IR (KBr, cm^{-1}): 3492, 3410, 3283 (NH_2), 1656 (C=O), 1582 (C=N), 1194, 1137 (C-F); MS (ESI), *m/z*: 372 ($M+H^+$); HRMS *m/z* calcd for $C_{14}H_{10}ClF_3N_5O_2$ ($M+H^+$), 372.0470; found, 372.0466.

General procedure for the synthesis of compounds 10a–g. The *N*-hydroxy-pyrazole-carboximidoyl chloride (1.0 mmol) and cyclic secondary amine (1.0 mmol) were dissolved in tetrahydrofuran and stirred for 15 min at room temperature. After completion of the reaction, adjusted the pH value of mixture to 7 using 10% NaOH

solution, added 20 mL water and stirred for 15 min. Then separated organic layer and dried over anhydrous Na_2SO_4, the solvent removed in vacuo and the residue purified by a column with silica gel using petroleum ether/ethyl acetate (8.5:1.5 v/v) mixture to obtain pure products of **10a–g**.

(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl) (piperidin-1-yl) methanone oxime (10a). White solid; yield: 0.24 g (59%); mp 162–164°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.52–1.64 (m, 6H), 3.08–3.15 (m, 4H), 6.88 (s, N–OH, 1H), 7.47–7.55 (m, 3H), 7.62 (d, J = 8.08 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.41, 25.19, 47.51, 109.77, 120.29 (q, ^1J = 270.59 Hz, CF_3), 125.21, 128.46, 129.19, 129.38, 137.16, 141.15 (q, ^2J = 38.42 Hz, CF_3), 150.47; IR (KBr, cm^{-1}): 3290 (N–OH), 1625 (C=N), 1135 (C-F); MS (ESI), *m/z*: 373 (M + H$^+$); HRMS *m/z* calcd for $C_{16}H_{17}ClF_3N_4O$(M + H$^+$), 373.1038; found, 373.1031.

(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl) (morpholine)methanone oxime(10b). Cream solid; yield: 0.24 g (70%); mp 135–137°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.40 (t, J = 5.29, 4H), 3.75 (t, J = 5.29, 4H), 7.50 (s, N–OH, 1H), 7.52–7.62 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 48.58, 66.90, 112.34, 120.20 (q, ^1J = 270.04 Hz, CF_3), 125.19, 129.30, 129.88, 129.63, 136.94, 139.82 (q, ^2J = 39.51 Hz, CF_3), 143.29; IR (KBr, cm^{-1}): 3379 (N–OH), 1627 (C=N), 1131 (C-F); MS (ESI), *m/z*: 375 (M + H); HRMS *m/z* calcd for $C_{15}H_{15}ClF_3N_4O_2$ (M + H$^+$), 375.0830; found, 375.0824.

(4-Benzylpiperdine-1-yl)(5-chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methanone oxime (10c). Cream solid; yield: 0.24 g (65%); mp 164–166°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.18–1.32 (m, 2H), 1.57–1.75 (m, 3H), 2.55 (d, J = 6.79 Hz, 2H), 2.67 (t, J = 12.27 Hz, 2H), 3.55 (d, J = 12.27 Hz, 2H), 7.13 (d, J = 6.98 Hz, 2H), 7.19 (d, J = 7.17 Hz, 1H), 7.27 (t, J = 6.79 Hz, 2H), 7.29 (s, N–OH, 1H), 7.48–7.56 (m, 3H), 7.58–7.63 (m, 2H); ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 31.24, 38.04, 43.00, 46.86, 109.70, 119.58 (q, ^1J = 270.68 Hz, CF_3), 125.21, 125.89, 128.19, 128.48, 129.03, 129.18, 129.39, 137.20, 140.14, 141.02 (q, ^2J = 38.18 Hz, CF_3), 150.26; IR (KBr, cm^{-1}): 3276 (N–OH), 1630 (C=N), 1131 (C-F); MS (ESI), *m/z*: 463 (M + H$^+$); HRMS *m/z* calcd for $C_{23}H_{23}ClF_3N_4O$(M + H$^+$), 463.1507; found, 463.1502.

(5-Chloro-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)(4-phenylpiperazin-1-yl) methanone oxime (10d). Cream solid; yield: 0.24 g (67%); mp 164–166°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.23–3.31 (m, 4H), 3.38–3.52 (m, 4H), 7.02 (s, N–OH, 1H), 7.10–7.16 (m, 2H), 7.33 (t, J = 7.78 Hz, 2H), 7.50–7.56 (m, 4H), 7.62 (d, J = 7.78 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 45.75, 48.29, 108.83, 115.74, 119.50 (q, ^1J = 269.74 Hz, CF_3), 119.66, 124.23, 127.71, 128.28, 128.44, 128.72, 136.13, 140.02 (q, ^2J = 38.14 Hz, CF_3), 147.74, 149.78; IR (KBr, cm^{-1}): 3258 (N–OH), 1597 (C=N), 1126 (C-F); MS (ESI), *m/z*: 450 (M + H$^+$); HRMS *m/z* calcd for $C_{21}H_{20}ON_5ClF_3$ (M + H$^+$), 450.1303; found, 450.1288.

(5-Chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)(piperidin-1-yl) methanone oxime (10e). White solid; yield 0.25 g (62%); mp 163–165°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.42–1.68 (m, 6H), 2.97–3.21 (m, 4H), 7.20 (s, N–OH, 1H), 7.38–7.62 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.27, 25.16, 47.65, 109.73, 120.11 (q, ^1J = 269.74 Hz, CF_3), 126.36, 128.61, 129.43,135.45, 135.55, 141.47 (q, ^2J = 39.05 Hz, CF_3), 149.97; IR (KBr, cm^{-1}): 3285 (N–OH), 1624 (C=N), 1139 (C-F); MS (ESI), *m/z*: 407 (M + H$^+$); HRMS *m/z* calcd for $C_{16}H_{16}ON_4Cl_2F_3$ (M + H$^+$), 407.0647; found, 407.0631.

(4-Benzylpiperdine-1-yl)(5-chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl) methanone oxime (10f). Cream solid; yield: 0.31 g (64%); mp 189–191°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.23–1.30 (m, 1H), 1.59–1.67 (m, 4H), 2.55 (d, J = 7.17 Hz, 2H), 2.65 (t, J = 12.51 Hz, 2H), 3.53 (d, J = 12.35 Hz, 2H), 6.69 (s, N–OH, 1H), 7.13 (d, J = 6.86 Hz, 2H), 7.19 (t, J = 7.32 Hz, 1H), 7.27 (t, J = 7.17 Hz, 2H), 7.50 (d, J = 9.00 Hz, 2H), 7.57 (d, J = 9.00 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 31.62, 38.08, 43.05, 48.38, 110.07, 119.95 (q, ^1J = 270.08 Hz, CF_3), 125.93, 126.39, 128.22, 128.43, 129.05, 129.44, 135.46, 135.65, 140.16, 141.54 (q, ^2J = 38.63 Hz, CF_3),150.36; IR (KBr, cm^{-1}): 3269 (N–OH), 1639 (C=N), 1147 (C-F); MS (ESI), *m/z*: 497 (M + H$^+$); HRMS *m/z* calcd for $C_{23}H_{22}Cl_2F_3N_4O$(M + H$^+$), 497.1118; found, 497.1113.

(5-chloro-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)(4-phenylpiperazin-1-yl) methanoneoxime (10g). Cream solid; yield: 0.33 g (69%); mp 179–181°C; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 3.16–3.24 (m, 4H), 3.30 (t, J = 5.03 Hz, 4H), 6.73 (s, N–OH, 1H), 6.89 (t, J = 7.32 Hz, 1H), 6.94 (d, J = 7.93 Hz, 2H), 7.28 (t, J = 7.32 Hz, 2H), 7.52 (d, J = 8.85 Hz, 2H), 7.59 (d, J = 8.85 Hz, 2H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 46.07, 48.14, 109.42, 119.55 (q, ^1J = 270.68 Hz, CF_3), 115.62, 119.26, 125.73, 127.85, 128.35, 128.70, 134.49, 134.88, 140.57 (q, ^2J = 39.61 Hz, CF_3), 147.79, 150.44; IR (KBr, cm^{-1}): 3289 (N–OH), 1649 (C=N), 1128 (C-F); MS (ESI), *m/z*: 484 (M + H$^+$); HRMS *m/z* calcd for $C_{21}H_{19}ON_5Cl_2F_3$ (M + H$^+$), 484.0913; found, 484.0904.

In vitro **antibacterial assay.** Standard sterilized filter paper disks (5 mm diameter) impregnated with a solution of the test compound in DMSO (1 mg/mL) was placed on agar plate seeded with the appropriate test organism in triplicate. Ciprofloxacin and cloxacillin were used as standard antibacterial drugs. DMSO alone was used as control as the same aforementioned concentration. The plates were incubated at 35°C for 1–2 days. Antibacterial activity was determined by measuring the diameter of the zone of inhibition surrounding microbial growth [30,31].

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