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Original article

Synthesis and biological evaluation of novel substituted 1,3,4-thiadiazole and 2,6-di aryl substituted imidazo [2,1-*b*] [1,3,4] thiadiazole derivatives

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ABSTRACT

A new series of *N*-[5-(4-(alkyl/aryl)-3-nitro-phenyl)-[1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide **4** (**a**–**l**) and 6-(4-Methoxy-phenyl)-2-(4-alkyl/aryl)-3-nitro-phenyl)-Imidazo [2,1-*b*] [1,3,4] thiadiazole **6** (**a**–**l**) were synthesized starting from 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine. The synthesized compounds were characterized by IR, NMR, mass spectral and elemental analysis. All the compounds were tested for antibacterial and antifungal activities. The antimicrobial activities of the compounds were assessed by well plate method (zone of inhibition). Compounds **4a**, **4c** and **6e**, **6g** displayed appreciable activity at the concentration 0.5–1.0 mg/mL.

1. Introduction

In last few decades, there is tremendous growth in the development of antimicrobial drugs. However development of the resistance against these antimicrobials is also at an alarming stage. During recent years, there have been intense investigation on thiadiazole and 2,6-imidazo [2,1-*b*] [1,3,4] thiadiazole compounds, many of which are known to possess interesting biological properties such antimicrobial [1] anti-inflammatory [2,3], anticonvulsant [4], antituberculosis [5,6], antifungal [7,8], antiviral [9], antibacterial [10–12], antitumour [13], anticancer [14,15] activities.

The various biological activities of imidazo [2,1-*b*] [1,3,4] thiadiazole and their derivatives have been known from early 1950s and since then, the research work on this heterocyclic system has led to significant developments in their chemistry and biology [16].

The literature review revealed that substituted 2-amino-5-aryl-1,3,4-thiadiazole analogues (Fig. 1) especially its phenyl substituent, exhibit significant *in-vitro* antiproliferative activity [17]. Moreover Levamisole appears to be the most effective in patient's drugs against small tumour burdens as it acts by stimulating the responsiveness of lymphocytes toward tumour antigens [18]. The 2,6-Aryl imidazo [2,1-*b*] thiazole derivatives of Levamisole and another 2,6-Aryl imidazo [1,2-*b*] [1,3,4] thiadiazole analogue has been reported as potential antitumour agents [19].

The continuous and widespread use of antimicrobial agents has resulted in the development of resistance to these drugs by pathogenic microorganisms, hence there is urgent need for newer class of drugs [20]. Thus, intense efforts in antimicrobial drug discovery are still needed to develop more promising and effective antifungal agents for use in the field of clinical research [21].

Prompted by the scope for the newer class of antimicrobial drugs and in continuation of our research on biologically active heterocycles [22,23], we hereby report the synthesis of some new 1,3,4-thiadiazole and 2,6-di aryl substituted imidazo [2,1-*b*] [1,3,4] thiadiazole derivatives. Moreover, nitrogen-containing heterocycles are also of broad pharmaceutical interest and significance,

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which justifies our continuing efforts in designing new heterocyclic molecules of biological importance [24].

2. Results and discussion

2.1. Chemistry

The title compounds were prepared according to the synthetic strategy described in Scheme 1. The key scaffold in the present study is 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine **2** and was synthesized from 4-Fluoro-3-nitrobenzoic acid by treating with phosphorous oxychloride and thiosemicarbazide using the reported procedure [25,26]. The compound was then converted into **3** by protecting $-NH_2$ group by pivaloyl chloride followed by treating different aliphatic/aromatic amines under microwave conditions to afford different substituted 1,3,4-Thiadiazole derivatives **4** (**a**–**l**).

Similarly the compound was also converted in to **5** by cyclization reaction with 4-methoxy phenacyl bromide according to the reported literature [27] and followed by Micro wave reaction using different amines to afford different substituted 2,6-Aryl imidazo [2,1-*b*] [1,3,4] thiadiazol **6** (**a**–**l**) derivatives (Scheme 1).

The formation of substituted 1,3,4-thiadiazole and 2,6-Aryl imidazo [2,1-*b*] [1,3,4]-thiadiazole derivatives were confirmed by recording their IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectral data. IR spectrum of **4a** shows absorption at 3516 cm^{-1} which is due to amide –NH stretch. An absorption band at 2933, 2836 cm^{-1} which is due to aromatic stretching, band at 1587 cm^{-1} is due to C=N group, band at 1461 cm^{-1} is stretching of phenyl rings. The ^{1}H NMR of compound **4a** showed broad singlet in the region of δ 12.18 cm^{-1}, which is due to amide –NH proton, the singlet at δ 8.33–8.32 cm^{-1}, multiplet in the region of δ 8.08–8.06 cm^{-1} and doublet in the region of δ 7.42–7.39 cm^{-1} with *J* value 8.76 Hz for the aromatic phenyl ring protons. In the aliphatic region, the multiplet observed in the region of δ 3.71–3.69 cm^{-1} and δ 3.10–3.08 cm^{-1} is due to the morpholine ring protons. Similarly singlet at δ 1.26 cm^{-1} for *tert*-butyl (9) protons. The mass spectrum of **4a** showed a molecular ion peak at $m/z = 392$ (M^+), which is in agreement with the molecular formula $C_{17}H_{21}N_5O_4S$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part.

Similarly IR spectrum of compound **6a** showed absorption at 2965, 2856 cm^{-1} which is due to aromatic stretching, band at 1614 cm^{-1} is due to C=N group, peak observed at 1486, 1465 cm^{-1} is stretching of phenyl rings. The ^{1}H NMR spectrum of compound **6a** showed singlet in the region of δ 8.60 due to the imidazole ring proton, the singlet at δ 8.31 multiplet in the region of δ 8.06–8.04 and doublet in the region of δ 7.44–7.42 with *J* value 8.72 Hz for aromatic nitro phenyl ring protons. The doublet appeared in the region of δ 7.81–7.79 and δ 6.99–6.96 due to methoxy phenyl protons. The multiplet observed in the region of δ 3.71–3.70 and δ 3.14–3.10 is due to morpholine ring protons. Similarly singlet at δ 3.77 is because of methoxy protons. The mass spectrum of compound **6a** showed a molecular ion peak at $m/z = 438$ (M^+), which is in agreement with the molecular formula $C_{21}H_{19}N_5O_4S$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part and the characterization is provided in Table 1 and Table 2.

2.2. Pharmacology

2.2.1. Antibacterial studies

The *in-vitro* antibacterial activity of newly synthesized compounds **4** (**a**–**l**) and **6** (**a**–**l**) was determined by well plate method [28,29]. The following Gram positive and negative bacteria were used as test organism: *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa* to investigate the activity. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 and 0.5 mg/mL.

The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains. The result indicated that among the synthesized compounds, **4a** and **6e** showed good activity against *E. coli* at concentrations of 1 and 0.5 mg/mL compared to standard drug Streptomycin. The remaining compounds showed moderated activity against all the three tested bacterial strains.

The details of antibacterial results are furnished in Table 3 and Table 4.

2.2.2. Antifungal activity

The fungal strains used in this study were *Candida albicans*, *Aspergillus flavus* and *Chrysosporium keratinophilum* because of their infectious nature. The study was determined by well plate method [30] at concentrations of 1, 0.5 mg/mL using DMSO solvent. Among the tested compounds, the compound **4c** and **6e** were emerged as active against *A. flavus* compared with standard drug Fluconazole. Whereas other compounds showed less activity against all the tested microorganisms compared to standard.

The result of antifungal studies have been furnished in Table 5 and Table 6

3. Conclusion

All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR studies. Compounds were screened for their *in-vitro* antibacterial and antifungal studies. Antibacterial activity for the derivatives **4** (**a**–**l**) and **6** (**a**–**l**) was evaluated by well plate method. The preliminary in-vitro antimicrobial screening of new 1,3,4-thiadiazole and imidazo [2,1-*b*] [1,3,4-thiadiazole derivatives, reported in the article, evidenced that many of the compounds from the both series have emerged as potent antibacterial and antifungal agents endowed with moderate to good activity. The possible improvements in the activity can be further achieved by slight modification of thiadiazole to imidazo [2,1-*b*][1,3,4-thiadiazole. Hence, it can be concluded that, new class of compounds certainly holds a greater pledge in discovering a potent antimicrobial agent.

More potent compounds among the synthesized series have been presented in Fig. 2.

4. Experimental

4.1. Chemistry

All the Chemicals were procured from Aldrich Co. Reactions were monitored and purity of the products was checked by TLC which was performed on MERCK 60F-254 silica gel plates. Melting

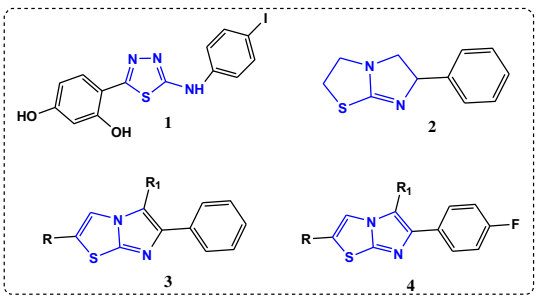
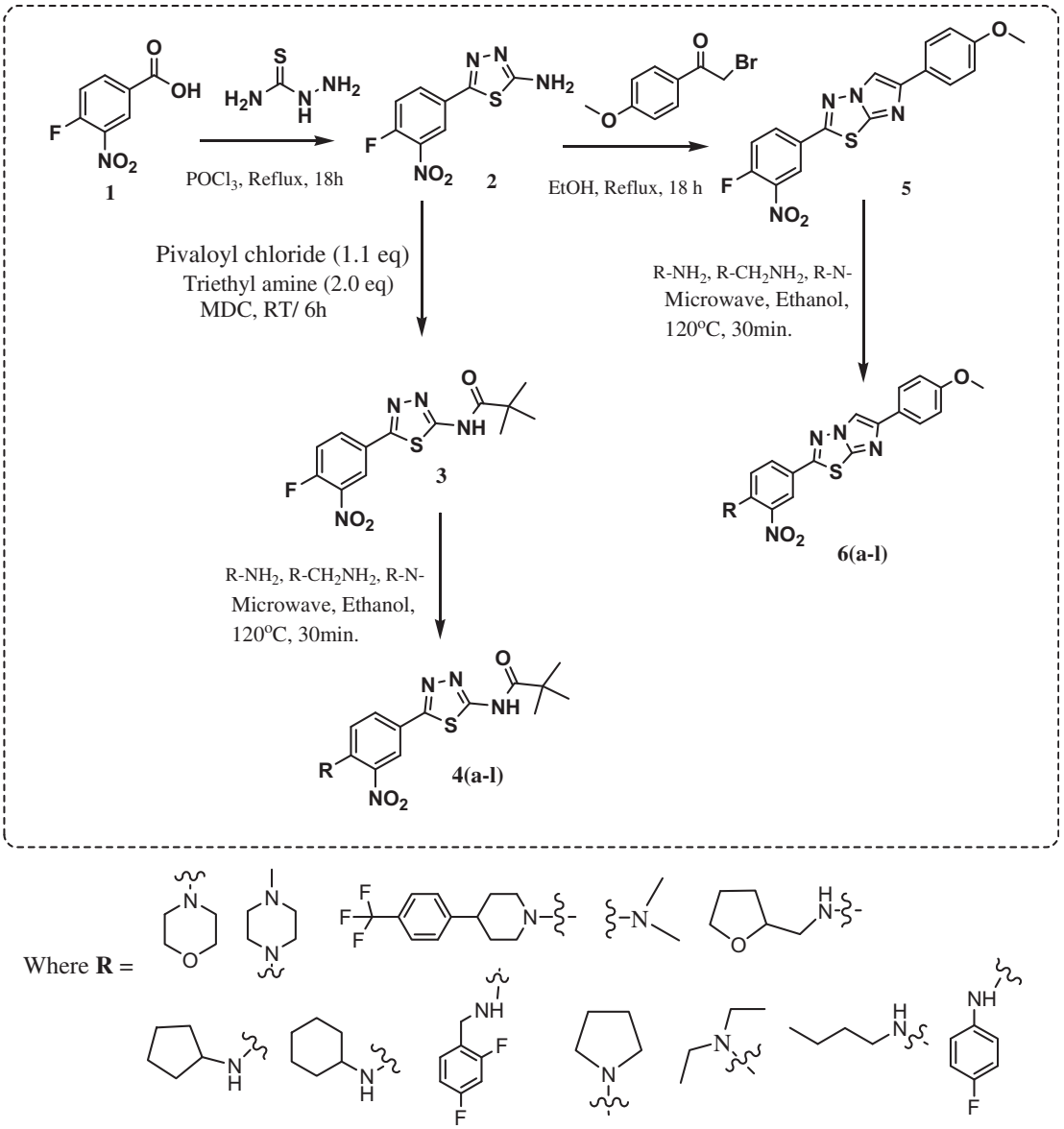


Fig. 1. Structures of some literature reviewed active molecules.



Scheme 1. Synthesis of the target compounds **4** (**a**–**l**) and **6** (**a**–**l**): (i) $POCl_3$, reflux, 18 h (ii) Pivaloyl chloride, TEA, RT, 6 h (iii) R–NH_2, EtOH, MW, 30 min (iv) 4-OMe-Phenacyl bromide, EtOH, reflux. (v) R–NH_2, EtOH, MW, 30 min.

points were determined on BUCHI Melting point B-545 instrument. The IR spectra (in KBr pellets) were recorded on NICOLET 6700FT-IR spectrophotomter. ^{1}H NMR spectra were recorded on BRUKER (400 MHz) spectrometer in DMSO-d_6 solvent. Mass spectra were recorded on LC-MS-Agilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min duration. The elemental analysis was performed on THERMO Finningan FLASH EA 1112 CHN analyzer. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co. (India) for compound purification.

*4.1.1. Preparation of 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine (**2**)*

To a stirred solution of 4-Fluoro-3-nitrobenzoic acid **1** (0.1081 mol) in phosphorous oxychloride (10 vol) was added thiosemicarbazide (0.2162 mol) and the reaction mixture was refluxed at 100 °C for 8 h. The reaction mixture was concentrated under high vacuum to remove the excess of phosphorous oxychloride and the residue was quenched with saturated sodium bicarbonate solution. The solid separated out was filtered and dried under high vacuum. The crude product was triturated with acetonitrile (200 mL) and filtered and dried to afford tilled compound **1** as a pale yellow solid (77.1%). Mp. 158–160 °C. ^{1}H NMR (DMSO-d_6): δ 8.42 (m, 1H, –Phenyl ring H), 8.15–8.11 (m, 1H, Phenyl ring H), 7.70–7.65 (m, 1H, phenyl ring H), 7.62 (s, 2H, $-NH_2$ proton). IR (KBr) cm^{-1}: 3160, 1670, 1540, 1346, 1298, 1146: MS: m/z = 241 (M^+).

*4.1.2. Preparation of N-[5-(4-Fluoro-3-nitro-phenyl)-[1,3,4-thiadiazole-2-yl]-2,2-dimethyl-propionamide (**3**)*

To a stirred solution of 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine **2** (0.0833 mol) in dry DCM (10 vol) was added triethyl amine (0.1666 mol) followed by pivaloyl chloride (0.0999 mol) in drops. After the addition, the reaction mixture was stirred at RT for 2 h. The reaction mixture was diluted with water (10 vol) and extracted with DCM. The organic layer was washed with brine (5 vol), dried over anhydrous Na_2SO_4 and concentrated

Table 1
Characterization data of the compounds **4** (**a**–**l**).

Com. no	R	Molecular formula (mol. wt.)	Melting point (°C)	Yield (%)
4a	Morpholine	$C_{17}H_{21}N_5O_4S$	168–170	80
4b	N-CH_3–Piperazine	$C_{18}H_{24}N_6O_3S$	170–172	90
4c	4-(CF_3)–Phenyl piperidine	$C_{25}H_{26}F_3N_5O_3S$	230–235	73
4d	Dimethyl	$C_{15}H_{19}N_5O_3S$	225–227	92
4e	Tetrahydro furfuryl	$C_{18}H_{23}N_5O_4S$	189–190	75
4f	Cyclopentyl	$C_{18}H_{23}N_5O_3S$	217–218	67
4g	Cyclohexyl	$C_{19}H_{25}N_5O_3S$	227–230	63
4h	2,4-Difluoro benzyl	$C_{20}H_{19}F_2N_5O_3S$	245–248	89
4i	Pyrrolidine	$C_{17}H_{21}N_5O_3S$	211–213	73
4j	Diethyl	$C_{17}H_{23}N_5O_3S$	242–243	85
4k	*n*-Butyl	$C_{17}H_{23}N_5O_3S$	250–253	85
4l	4-*F*-Phenyl	$C_{19}H_{18}FN_5O_3S$	210–215	93

Table 2
Characterization data of the compounds **6** (**a**–**l**).

Com. no	R	Molecular formula (mol. wt.)	Melting point (°C)	Yield (%)
6a	Morpholine	$C_{21}H_{19}N_5O_4S$	218–219	86
6b	N-CH_3–Piperazine	$C_{22}H_{22}N_6O_3S$	201–205	90
6c	4-(CF_3)–Phenyl piperidine	$C_{29}H_{24}F_3N_5O_3S$	260–265	76
6d	Dimethyl	$C_{19}H_{17}N_5O_3S$:	170–171	63
6e	Tetrahydro furfuryl	$C_{22}H_{20}N_4O_4S$	199–200	89
6f	Cyclopentyl	$C_{22}H_{21}N_5O_3S$	210–211	67
6g	Cyclohexyl	$C_{23}H_{23}N_5O_3S$	216–218	67
6h	2,4-Difluoro benzyl	$C_{24}H_{17}F_2N_5O_3S$	235–238	89
6i	Pyrrolidine	$C_{21}H_{19}N_5O_3S$	225–228	95
6j	Diethyl	$C_{21}H_{21}N_5O_3S$	196–197	90
6k	*n*-Butyl	$C_{21}H_{21}N_5O_3S$	203–204	92
6l	4-*F*-Phenyl	$C_{23}H_{16}FN_5O_3S$	220–225	93

under high vacuum. The solid obtained was purified by column chromatography using silica gel 60–120 mesh size and petroleum ether: ethyl acetate as eluent to afford the title compound as a pale yellow solid (85%).

Mp. 180–182 °C. ^{1}H NMR (DMSO-d_6): δ 12.48 (bs, 1H, –NH H), 8.63–8.61 (m, 1H, Phenyl ring H), 8.34–8.31 (s, 1H, phenyl ring H), 7.78 (s, 1H, –phenyl ring H), 1.27 (s, 9H). IR (KBr) cm^{-1}: 3159, 2930, 1688, 1540, 1346, 1298, 1146: MS: m/z = 325 (M^+).

4.2. General procedure for preparation N-[5-(4-(substituted)-3-nitro-phenyl)-[1,3,4-thiadiazole]-2,2-dimethyl-propionamide **4** (**a**–**l**)

To a solution of *N*-[5-(4-Fluoro-3-nitro-phenyl)-[1,3,4-thiadiaol-2-yl]-2,2-dimethyl-propionamide **3** in absolute ethanol (10 vol) was added different aromatic/aliphatic amines (1.1 eq) in a 20 mL microwave vessel and irradiated with microwave at 100 °C for 1 h using Biotage MW instrument. The solid separated out was filtered and washed with cold ethanol, dried under vacuum to afford titled compounds **4** (**a**–**l**) as pale yellow/orange solid (80–90% yield).

4.2.1. 2,2-Dimethyl-N-[5-(4-morpholin-4-yl-3-nitro-phenyl)-[1,3,4] thiadiazo-2-yl]-propionamide (**4a**)

IR (KBr) cm^{-1}: 3516, 2933, 2836, 1621, 1587, 1510, 1461, 1217, 1123; MS: m/z = 392 (M^+); ^{1}H NMR (DMSO-d_6): 12.18 (bs, 1H, –NH H), 8.33–8.32 (s, 1H, Ar–H), 8.08–8.06 (m, 1H, Ar–H), 7.42–7.39 (d, 1H, J = 8.76 Hz, Ar–H), 3.71–3.69 (m, 4H, morpholine H), 3.10–3.08 (m, 4H, morpholine H), 1.26 (s, 9H, -*tert*-Butyl H); ^{13}C NMR (DMSO-d_6) 176.85, 159.75, 159.22, 146.03, 141.21, 131.80, 123.90, 122.63, 121.55, 65.87, 50.82, 26.46. Anal. Calcd. (Found) for $C_{17}H_{21}N_5O_4S$: C, 52.16 (52.18); H, 5.41 (5.43); N, 17.89 (17.75).

4.2.2. 2,2-Dimethyl-N-{5-[4-(4-methyl-piperazin-1-yl)-3-nitro-phenyl]-[1,3,4]thiadiazol-2-yl}-propionamide (**4b**)

IR (KBr) cm^{-1}: 3133, 2933, 2805, 1687, 1541, 1453, 1386, 1399, 1299, 1170; MS: m/z = 405 (M^+); ^{1}H NMR (DMSO-d_6): 12.35 (bs, 1H, –NH H), 8.30 (s, 1H, Ar–H), 8.05–8.02 (m, 1H, Ar–H), 7.39–7.37 (d, 1H, J = 8.84 Hz, Ar–H), 3.10–3.08 (m, 4H, –piperazine H), 2.50–2.48 (m, 4H, –piperazine H), 2.2 (s, 3H, –methyl H), 1.26 (s, 9H, -*tert*-Butyl H); ^{13}C NMR (DMSO-d_6) 176.84, 159.81, 159.14, 146.1, 140.9, 131.6, 123.9, 122.0, 121.5, 54.2, 50.32, 45.6, 26.47. Anal. Calcd. (Found) for $C_{18}H_{24}N_6O_3S$: C, 53.45 (53.55); H, 5.98 (5.99); N, 20.78 (20.69).

4.2.3. 2,2-Dimethyl-N-(5-{3-nitro-4-[4-(4-trifluoromethyl-phenyl)-piperdin-1-yl]-phenyl}-[1,3,4] thiadiazol-2-yl)-propionamide (**4c**)

IR (KBr) cm^{-1}: 3155, 2932, 1687, 1614, 1522, 1350, 1323, 1110, 1068; MS: m/z = 534 (M^+); ^{1}H NMR (DMSO-d_6): 12.10 (bs, 1H, –NH H), 8.32 (s, 1H, Ar–H), 8.06–8.04 (d, 1H, J = 8.36 Hz, Ar–H), 7.68–7.66 (d, 2H, J = 7.76 Hz, Ar–H), 7.53–7.51 (d, 2H, J = 7.80 Hz, Ar–H), 7.45–7.43 (d, 1H, J = 8.06 Hz, Ar–H), 3.43–3.40 (m, 2H), 3.11–3.05 (m, 2H), 2.88–2.84 (m, 1H), 1.90–1.87 (m, 2H), 1.82–1.74 (m, 2H), 1.26 (s, 9H, -*tert*-Butyl H); ^{13}C NMR (DMSO-d_6) 176.9, 159.7, 159.31, 150.3, 146.5, 140.6, 131.7, 127.6, 127.4, 127.1, 126.8, 125.7, 125.29, 125.25, 124.0, 123.01, 121.86, 121.75, 51.2, 32.37, 26.5.Anal. Calcd. (Found) for $C_{25}H_{26}F_3N_5O_3S$: C, 56.28 (56.29); H, 4.91 (4.92); N, 13.13 (13.10).

4.2.4. N-[5-(4-Dimethylamino-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4d**)

IR (KBr) cm^{-1}: 3137, 2928, 1690, 1613, 1504, 1431, 1339, 1297, 1148; MS: m/z = 350 (M^+); ^{1}H NMR (DMSO-d_6): 12.31 (bs, 1H, –NH H), 8.24 (s, 1H, Ar–H), 7.98–7.96 (t, 1H, J = 7.88 Hz), 7.28–7.26 (d,

Table 3
Antibacterial activity of compounds **4** (**a**–**l**).

Organic com.	*Escherichia coli*		*Bacillus subtilis*		*Pseudomonas aeroginosa*	
Conc. in mg/mL	1	0.5	1	0.5	1	0.5
Streptomycin	19 ± 0.2	17 ± 0.3	22 ± 0.6	19 ± 0.6	19 ± 0.5	15 ± 0.3
Control	00	00	00	00	00	00
4a	12 ± 0.5	10 ± 0.4	11 ± 0.2	09 ± 0.6	13 ± 0.3	10 ± 0.3
4b	05 ± 0.4	03 ± 0.2	04 ± 0.3	03 ± 0.2	03 ± 0.1	02 ± 0.3
4c	08 ± 0.3	05 ± 0.5	07 ± 0.3	05 ± 0.4	07 ± 0.2	06 ± 0.1
4d	–	–	–	–	–	–
4e	–	–	–	–	–	–
4f	06 ± 0.6	04 ± 0.3	04 ± 0.4	03 ± 0.4	03 ± 0.4	02 ± 0.2
4g	10 ± 0.4	08 ± 0.5	08 ± 0.2	06 ± 0.5	09 ± 0.5	07 ± 0.3
4h	05 ± 0.4	03 ± 0.3	04 ± 0.2	02 ± 0.6	04 ± 0.2	02 ± 0.2
4i	05 ± 0.3	03 ± 0.1	03 ± 0.3	01 ± 0.2	06 ± 0.5	04 ± 0.2
4j	–	–	–	–	–	–
4k	–	–	–	–	–	–
4l	07 ± 0.4	05 ± 0.3	05 ± 0.4	03 ± 0.3	06 ± 0.4	04 ± 0.2

Table 4
Antifungal activity of compounds **4** (**a**–**l**).

Organic comp.	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
	Diameter of zone of inhibition (mm)					
Conc. in mg/mL	1	0.5	1	0.5	1	0.5
Control	00		00		00	
Standard fluconazole	13 ± 0.2	10 ± 0.1	17 ± 0.2	15 ± 0.2	22 ± 0.2	20 ± 0.2
4a	05 ± 0.4	02 ± 0.5	04 ± 0.6	02 ± 0.3	05 ± 0.4	03 ± 0.2
4b	03 ± 0.4	–	04 ± 0.5	02 ± 0.3	04 ± 0.6	02 ± 0.3
4c	08 ± 0.7	05 ± 0.4	07 ± 0.4	05 ± 0.3	07 ± 0.3	04 ± 0.2
4d	–	–	–	–	–	–
4e	–	–	–	–	–	–
4f	04 ± 0.3	02 ± 0.2	04 ± 0.5	02 ± 0.3	05 ± 0.3	02 ± 0.6
4g	07 ± 0.6	05 ± 0.3	06 ± 0.3	04 ± 0.8	09 ± 0.5	07 ± 0.6
4h	06 ± 0.4	04 ± 0.3	07 ± 0.4	05 ± 0.5	05 ± 0.7	03 ± 0.2
4i	06 ± 0.8	04 ± 0.2	05 ± 0.3	03 ± 0.5	06 ± 0.2	05 ± 0.7
4j	–	–	–	–	–	–
4k	–	–	–	–	–	–
4l	03 ± 0.4	02 ± 0.1	05 ± 0.3	04 ± 0.2	04 ± 0.6	02 ± 0.4

1H, $J = 8.88$ Hz, Ar–H), 2.90 (s, 6H), 1.26 (s, 9H, -*tert*-Butyl H); ^{13}C NMR (DMSO-d_6) 176.71, 160.19, 158.59, 146.40, 137.19, 131.30, 124.60, 118.71, 118.59, 41.90, 26.47. Anal. Calcd. (Found) for $C_{15}H_{19}N_5O_3S$: C, 51.56 (51.57); H, 5.48 (5.60); N, 20.04 (20.00).

4.2.5. 2,2-Dimethyl-N-(5-{3-nitro-4-[tetrahydro-furan-2-ylmethyl)-amino]-phenyl}-[1,3,4] thiadiazol-2-yl)-propionamide (**4e**)

IR (KBr) cm^{-1}: 3369, 2932, 1685, 1625, 1527, 1459, 1298, 1218, 1151, 1073; MS: $m/z = 406$ (M^+); ^{1}H NMR (DMSO-d_6): 12.20 (bs, 1H, –NH H), 8.51 (s, 1H, Ar–H), 8.50–8.44 (m, 1H), 8.03–8.00 (m, 1H), 7.26–7.23 (d, 1H, $J = 9.24$ Hz, Ar–H), 4.12–4.10 (m, 1H), 3.8–3.77 (m, 1H), 3.70–3.67 (m, 1H), 3.56–3.55 (m, 1H), 3.43–3.41 (m, 1H), 20–1.98 (m, 1H), 1.88–1.83 (m, 2H), 1.65–1.62 (m, 2H), 1.26 (s, 9H). ^{13}C NMR (DMSO-d_6) 176.68, 160.28, 158.39, 146.07, 134.11, 130.72, 124.25, 117.34, 116.00, 76.53, 67.46, 46.35, 28.47, 26.46, 25.25. Anal. Calcd. (Found) for $C_{18}H_{23}N_5O_4S$: C, 53.32 (53.35); H, 5.72 (5.73); N, 17.27 (17.15).

4.2.6. N-[5-(4-Cyclopentylamino-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4f**)

IR (KBr) cm^{-1}: 3370, 3160, 2925, 1675, 1681, 1572, 1530, 1463, 1287, 1240, 1153; MS: $m/z = 390$ (M^+); ^{1}H NMR (DMSO-d_6): 12.31 (bs, 1H, –NH H), 8.53 (s, 1H, Ar–H), 8.19–8.17 (d, 1H, $J = 6.6$ Hz, Ar–H), 8.06–8.03 (m, 1H), 7.26–7.24 (d, 1H, $J = 9.24$ Hz, Ar–H), 4.15 (m, 1H), 2.12–2.06 (m, 2H), 1.74–1.63 (m, 6H), 1.61–1.58 (m, 1H), 1.47 (s, 9H), 1.26 (s, 9H). Anal. Calcd. (Found) for $C_{18}H_{23}N_5O_3S$: C, 55.51 (55.52); H, 5.95 (5.98); N, 17.98 (17.96).

4.2.7. N-[5-(4-Cyclohexylamino-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4g**)

IR (KBr) cm^{-1}: 3362, 3140, 2931, 1685, 1621, 1562, 1530, 1463, 1297, 1240, 1153; MS: $m/z = 404$ (M^+); ^{1}H NMR (DMSO-d_6): 11.62 (bs, 1H, –NH H), 8.50 (s, 1H, Ar–H), 8.20–8.18 (d, 1H, $J = 7.7$ Hz, Ar–H), 8.03–8.00 (m, 1H), 7.28–7.23 (d, 1H, $J = 9.24$ Hz, Ar–H), 3.71 (bs, 1H), 1.98–1.95 (m, 2H), 1.72–1.69 (m, 2H), 1.61–1.58 (m, 2H), 1.47–1.35 (m, 4H), 1.26 (s, 10H). Anal. Calcd. (Found) for $C_{19}H_{25}N_5O_3S$: C, 56.56 (56.60); H, 6.25 (6.27); N, 17.36 (17.30).

4.2.8. N-{5-[4-(2,4-Difluoro-benzylamino)-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4h**)

IR (KBr) cm^{-1}: 3332, 3278, 3141, 2976, 1675, 1632, 1528, 1505, 1300, 1104; MS: $m/z = 4448$ (M^+); ^{1}H NMR (DMSO-d_6): 10.21 (bs, 1H, –NH H), 8.86–8.83 (t, 1H, $J = 6.28$ Hz), 8.56 (s, 1H), 7.99–7.96 (m, 1H), 7.43–7.37 (m, 1H), 7.31–7.25 (m, 1H), 7.06–7.02 (m, 2H), 4.72 (d, 2H, $J = 6.12$ Hz), 1.25 (s, 9H). ^{13}C NMR (DMSO-d_6) 176.75, 162.83, 162.70, 161.36, 161.24, 160.39, 160.26, 160.16, 158.91, 158.78, 158.55, 145.34, 134.20, 131.52, 130.05, 129.99, 129.95, 129.90, 124.38, 121.21, 121.18, 121.07, 121.03, 117.79, 115.60, 111.70, 111.67, 111.49, 111.46, 104.27, 104.02, 103.76, 26.47. Anal. Calcd. (Found) for $C_{20}H_{19}F_2N_5O_3S$: C, 53.68 (53.69); H, 4.28 (4.30); N, 15.65 (15.55).

4.2.9. N-[5-(3-Nitro-4-pyrrolidin-1-yl-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4i**)

IR (KBr) cm^{-1}: 3380, 3140, 2975, 1655, 1651, 1592, 1539, 1465, 1283, 1240, 1157; MS: $m/z = 376$ (M^+); ^{1}H NMR (DMSO-d_6): 11.60

Table 5
Antibacterial activity of compounds **6** (**a**–**l**).

Organic compound	*Escherichia coli*		*Bacillus subtilis*		*Pseudomonas aeruginosa*	
Conc. in mg/mL	1	0.5	1	0.5	1	0.5
Streptomycin	19 ± 0.2	17 ± 0.3	22 ± 0.6	19 ± 0.6	19 ± 0.5	15 ± 0.3
Control	00	00	00	00	00	00
6a	–	–	–	–	–	–
6b	06 ± 0.6	04 ± 0.3	05 ± 0.2	03 ± 0.6	05 ± 0.5	03 ± 0.2
6c	–	–	–	–	–	–
6d	04 ± 0.5	03 ± 0.2	03 ± 0.7	02 ± 0.3	06 ± 0.4	04 ± 0.5
6e	13 ± 0.1	10 ± 0.7	10 ± 0.6	08 ± 0.8	13 ± 0.6	09 ± 0.2
6f	–	–	–	–	–	–
6g	11 ± 0.5	09 ± 0.7	10 ± 0.7	07 ± 0.4	09 ± 0.1	07 ± 0.7
6h	03 ± 0.4	01 ± 0.1	04 ± 0.3	02 ± 0.1	04 ± 0.8	02 ± 0.3
6i	08 ± 0.2	05 ± 0.3	09 ± 0.7	07 ± 0.6	06 ± 0.4	04 ± 0.5
6j	06 ± 0.4	04 ± 0.6	05 ± 0.4	03 ± 0.4	03 ± 0.2	01 ± 0.4
6k	05 ± 0.6	03 ± 0.5	06 ± 0.3	04 ± 0.6	07 ± 0.3	05 ± 0.8
6l	–	–	–	–	–	–

Table 6
Antifungal activity of compounds **6** (**a**–**l**).

	Aspergillus flavus		*Chrysosporium keratinophilum*		*Candida albicans*	
	Diameter of zone of inhibition (mm)					
Conc. in mg/mL	1	0.5	1	0.5	1	0.5
Control	00		00		00	
Standard fluconazole	13 ± 0.2	10 ± 0.1	17 ± 0.2	15 ± 0.2	22 ± 0.2	20 ± 0.2
6a	–	–	–	–	–	–
6b	–	–	–	–	–	–
6c	–	–	–	–	–	–
6d	04 ± 0.2	02 ± 0.1	04 ± 0.5	02 ± 0.2	05 ± 0.7	03 ± 0.3
6e	09 ± 0.5	06 ± 0.4	08 ± 0.3	06 ± 0.5	07 ± 0.4	05 ± 0.5
6f	–	–	–	–	–	–
6g	08 ± 0.5	06 ± 0.4	07 ± 0.3	05 ± 0.5	09 ± 0.3	07 ± 0.2
6h	06 ± 0.2	03 ± 0.5	08 ± 0.7	06 ± 0.5	05 ± 0.4	03 ± 0.2
6i	07 ± 0.1	05 ± 0.2	06 ± 0.5	04 ± 0.3	07 ± 0.3	05 ± 0.6
6j	05 ± 0.4	03 ± 0.3	05 ± 0.6	03 ± 0.2	06 ± 0.4	05 ± 0.3
6k	02 ± 0.4	–	03 ± 0.2	01 ± 0.2	03 ± 0.5	02 ± 0.3
6l	–	–	–	–	–	–

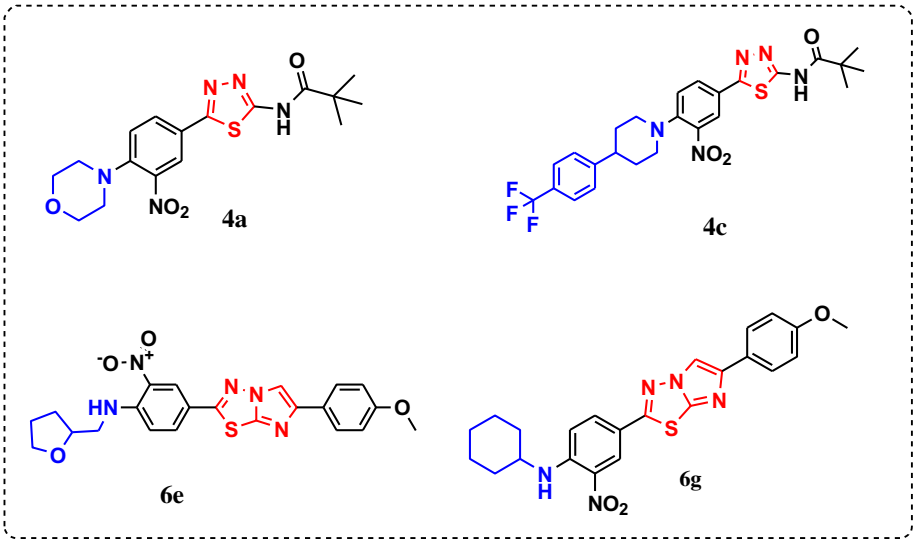


Fig. 2. More potent compounds among the synthesized series.

(bs, 1H, –NH H), 8.52 (s, 1H, Ar–H), 8.23–8.19 (d, 1H, J = 7.7 Hz, Ar–H), 7.26–7.21 (d, 1H, J = 9.24 Hz, Ar–H), 3.23–3.25 (m, 4H), 1.95–1.92 (m, 4H), 1.26 (s, 9H). Anal. Calcd. (Found) for $C_{17}H_{21}N_5O_3S$: C, 54.38 (55.40); H, 5.64 (5.66); N, 18.65 (18.67).

*4.2.10. N-[5-(4-Diethylamino-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4j**)*

IR (KBr) cm^{-1}: 3345, 3145, 2875, 1689, 1690, 1592, 1589, 1465, 1293, 1240, 1157; MS: m/z = 378 (M^+); ^{1}H NMR (DMSO-d_6): 11.62 (bs, 1H, –NH H), 8.54 (s, 1H, Ar–H), 8.23-8.19 (d, 1H, J = 7.7 Hz, Ar–H), 7.28–7.22 (d, 1H, J = 9.3 Hz, Ar–H), 3.23–3.24 (m, 4H), 1.25 (s, 9H), 1.15–1.08 (m, 6H). Anal. Calcd. (Found) for $C_{17}H_{23}N_5O_3S$: C, 54.09 (54.10); H, 6.14 (6.15); N, 18.55 (18.57).

*4.2.11. N-[5-(4-Butylamino-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4k**)*

IR (KBr) cm^{-1}: 3386, 3147, 2977, 1655, 1659, 1572, 1579, 1475, 1253, 1230, 1197; MS: m/z = 378 (M^+); ^{1}H NMR (DMSO-d_6): 11.52 (bs, 1H, –NH H), 8.55 (s, 1H, Ar–H), 8.21–8.18 (d, 1H, J = 7.6 Hz, Ar–H), 7.26–7.20 (d, 1H, J = 9.2 Hz, Ar–H), 3.47–3.42 (m, 2H), 1.66–1.59 (m, 4H), 1.26 (s, 9H), 0.94 (m, 3H). Anal. Calcd. (Found) for $C_{17}H_{23}N_5O_3S$: C, 54.09 (54.11); H, 6.14 (6.16); N, 18.55 (18.54).

*4.2.12. N-{5-[4-(4-Fluoro-phenylamino)-3-nitro-phenyl)-[1,3,4] thiadiazol-2-yl]-2,2-dimethyl-propionamide (**4l**)*

IR (KBr) cm^{-1}: 3165, 2962, 1687, 1644, 1542, 1350, 1373, 1170, 1064; MS: m/z = 416 (M^+); ^{1}H NMR (DMSO-d_6): 12.10 (bs, 1H, –NH H), 8.32 (s, 1H, Ar–H), 8.06–8.04 (d, 1H, J = 8.36 Hz, Ar–H), 7.68–7.66 (d, 2H, J = 7.76 Hz, Ar–H), 7.53–7.51 (d, 2H, J = 7.80 Hz, Ar–H), 7.45–7.43 (d, 1H, J = 8.06 Hz, Ar–H), 1.26 (s, 9H, -*tert*-Butyl H); Anal. Calcd. (Found) for $C_{19}H_{18}FN_5O_3S$: C, 54.93 (54.97); H, 4.37 (4.38); N, 16.86 (16.88).

*4.3. Preparation of 2-(4-Fluoro-3-nitro-phenyl)-6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazole (**5**)*

To a solution of 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine (0.0416 mol) in absolute ethanol (10 vol) was added 4-methoxy phenacyl bromide (0.049 mol) at RT. The reaction mixture was heated to 80 °C for 18 h. After the completion of the reaction, the reaction mixture was concentrated through high vacuum. The residue was triturated with acetonitrile and filtered, dried to afford the title compound (77.8%) as yellow solid.

IR (KBr) cm^{-1}: 3526, 2923, 2836, 1661, 1587, 1560, 1461, 1287, 1153; MS: m/z = 371 (M^+); ^{1}H NMR (DMSO-d_6): 8.62 (s, 1H, Ar–H), 8.56–8.54 (m, 1H, Ar–imidazole H), 8.32–8.29 (m, 1H, Ar–H), 7.81–7.76 (m, 3H, Ar–H), 6.97–6.93 (m, 2H, Ar–H), 3.77 (s, 3H, –methoxy H).

^{13}C NMR (DMSO-d_6) 158.79, 157.61, 157.33, 154.68, 145.93, 144.34, 137.46, 137.38, 134.10, 134.0, 126.70, 126.66, 126.13, 126.03, 124.01, 120.13, 119.91, 114.02, 109.49, 55.07. Anal. Calcd. (Found) for $C_{17}H_{11}N_4O_3S$: C, 55.13 (55.15); H, 2.99 (3.05); N, 15.13 (15.12).

4.4. General procedure for preparation of 6-(4-methoxy-phenyl)-2-(4-substituted)-3-nitro-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazole **6** (**a**–**l**)

To a stirred solution of 2-(4-Fluoro-3-nitro-phenyl)-6-(4-methoxy-phenyl)-imidazo [2,1-*b*] [1,3,4] thiadiazole in absolute ethanol (10 vol) was added different aromatic/aliphatic amines (1.1 eq) in a 20 mL microwave vessel and irradiated microwave at 100 °C for 1 h using Biotage MW instrument. The solid separated out was filtered and washed with cold ethanol, dried under vacuum to afford titled compounds **6** (**a**–**l**) as pale yellow/orange solid (80–90% yield).

4.4.1. 6-(4-Methoxy-phenyl)-2-[4-morpholin-4-1-yl)-3-nitro-phenyl]-imidazo [2,1-b] [1,3,4-thiadiazole (**6a**)

IR (KBr) cm^{-1}: 3134, 2965, 2856, 1614, 1514, 1486, 1465, 1333, 1247, 1112, 1019; MS: m/z = 438 (M^+); ^{1}H NMR (DMSO-d_6): 8.60 (s, 1H, Ar–imidazole H), 8.31 (s, 1H, Ar–H), 8.06–8.04 (m, 1H), 7.81–7.79 (d, 2H, J = 8.4 Hz, Ar–H), 7.44–7.42 (d, 1H, J = 8.72 Hz, Ar–H), 6.99–6.96 (d, 2H, J = 8.5 Hz, Ar–H), 3.77 (s, 3H), 3.71–3.70 (m, 4H), 314–3.10 (m, 4H); ^{13}C NMR (DMSO-d_6) 158.74, 146.77, 145.60, 144.0, 140.28, 131.27, 126.35, 126.00, 124.31, 121.34, 121.05, 114.08, 109.41, 65.76, 55.10, 50.56. Anal. Calcd. (Found) for $C_{21}H_{19}N_5O_4S$: C, 57.66 (57.68); H, 4.38 (4.39); N, 16.01 (15.99).

4.4.2. 6-(4-Methoxy-phenyl)-2-[4-(4-methyl-piperazin-1-yl)-3-nitro-phenyl]-imidazo [2,1-b] [1,3,4] thiadiazole (**6b**)

IR (KBr) cm^{-1}: 3083, 2940, 2805, 1611, 1521, 1490, 1340, 1240; MS: m/z = 451 (M^+); ^{1}H NMR (DMSO-d_6): 8.59 (s, 1H, Ar–imidazole H), 8.28 (s, 1H, Ar–H), 8.03–8.00 (m, 1H), 7.80–7.78 (d, 2H, J = 8.8 Hz, Ar–H), 7.43–7.40 (d, 1H, J = 8.92 Hz, Ar–H), 6.98–6.96 (d, 1H, J = 8.88 Hz, Ar–H), 3.77 (s, 3H), 3.16–3.13 (m, 4H, piperazine H), 2.44–2.41 (m, 4H, –piperazine H), 2.21 (s, 3H); ^{13}C NMR (DMSO-d_6) 158.84, 158.74, 146.84, 145.57, 143.98, 140.04, 131.17, 126.37, 126.01, 124.36, 121.37, 120.53, 114.09, 109.41, 55.11, 54.16, 50.11, 45.60. Anal. Calcd. (Found) for $C_{22}H_{22}N_6O_3S$: C, 58.65 (58.64); H, 4.92 (4.95); N, 18.65 (18.59).

4.4.2.1. 6-(4-Methoxy-phenyl)-2-{3-nitro-4-[4-(4-trifluoromethyl-phenyl)-piperidine-1-yl]-phenyl}-imidazo [2,1-b] [1,3,4] thiadiazole (**6c**).

IR (KBr) cm^{-1}: 3145, 2942, 1677, 1674, 1572, 1330, 1333, 1130, 1088; MS: m/z = 580 (M^+); ^{1}H NMR (DMSO-d_6): 8.62 (s, 1H), 8.56–8.54 (m, 1H), 8.32–8.29 (m, 1H), 7.81–7.77 (m, 3H), 7.68–7.66 (d, 2H, J = 7.7 Hz), 7.53–7.51 (d, 2H, J = 7.8 Hz), 6.93–6.90 (m, 2H), 3.7 (s, 3H), 3.43–3.40 (m, 2H), 3.11–3.0 (m, 2H), 2.80 (m, 1H), 1.90–1.87 (m, 2H), 1.82–1.74 (m, 2H); Anal. Calcd. (Found) for $C_{29}H_{24}F_3N_5O_3S$: C, 60.10 (60.12); H, 4.17 (4.18); N, 12.08 (12.07).

4.4.3. {4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-dimethyl-amine (**6d**)

IR (KBr) cm^{-1}: 3133, 2928, 1690, 1613, 1504, 1431, 1339, 1297, 1148; MS: m/z = 396 (M^+); ^{1}H NMR (DMSO-d_6): 8.57 (s, 1H), 8.20 (s 1H), 7.98–7.95 (m, 1H), 7.80–7.78 (d, 1H, J = 8.7 Hz), 7.38–7.36 (d, 2H, J = 8.5 Hz), 6.96–6.94 (m, 2H), 3.78 (s, 3H), 2.9 (s, 6H). Anal. Calcd. (Found) for $C_{19}H_{17}N_5O_3S$: C, 57.71 (57.68); H, 4.33 (4.35); N, 17.71 (17.70).

4.4.4. {4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-(tetrahydro-furan-2-ylmethyl)-amine (**6e**)

IR (KBr) cm^{-1}: 3469, 2832, 1785, 1625, 1527, 1459, 1298, 1218, 1191, 1083; MS: m/z = 452.5 (M^+); ^{1}H NMR (DMSO-d_6): 8.58 (s, 1H), 8.20 (s, 1H), 7.98–7.95 (m, 1H), 7.81–7.79 (d, 2H, J = 8.76 Hz), 7.40–7.38 (1H, d, J = 9 Hz), 6.99–6.97 (m, 2H), 4.15–4.1 (m, 1H), 4.09–3.7 (m, 1H), 3.7 (s, 3H), 3.68–3.55 (m, 1H), 3.50–3.39 (m, 1H), 3.32–3.30 (m, 1H), 2.5–2.48 (m, 1H), 2.00–1.96 (m, 2H), 1.88–1.83 (m, 1H). Anal. Calcd. (Found) for $C_{22}H_{21}N_5O_4S$: C, 58.52 (58.54); H, 4.69 (4.66); N, 15.51 (15.50).

4.4.5. Cyclopentyl-{4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-amine (**6f**)

IR (KBr) cm^{-1}: 3351, 3128, 2957, 2867, 1619, 1538, 1464, 1409, 1236, 1171; MS: m/z = 436 (M^+); ^{1}H NMR (DMSO-d_6): 8.58 (s, 1H), 8.51 (s, 1H), 8.29–8.27 (d, 1H, J = 6.48 Hz), 8.04–8.02 (m, 1H), 7.80–7.78 (d, 2H, J = 8.5 Hz), 7.31–7.29 (d, 1H, J = 9.36 Hz), 6.99–6.97 (d, 2H, J = 8.64 Hz), 4.16–4.15 (m, 1H), 3.78 (s, 3H), 2.11–2.10 (m, 2H), 1.73–1.72 (m, 2H), 1.68–1.56 (m, 4H). Anal. Calcd. (Found) for $C_{22}H_{21}N_5O_3S$: C, 60.67 (60.68); H, 4.86 (4.88); N, 16.08 (16.05).

4.4.6. Cyclohexyl-{4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-amine (**6g**)

IR (KBr) cm^{-1}: 3361, 3178, 2967, 2897, 1699, 1578, 1434, 1439, 1296, 1171; MS: m/z = 450 (M^+); ^{1}H NMR (DMSO-d_6): 8.69 (s, 1H), 8.60 (s, 1H), 8.37–8.35 (d, 1H, J = 8.4 Hz), 8.31–8.29 (d, 1H, J = 8.64 Hz), 8.02–7.99 (d, 2H, J = 10.64 Hz), 7.00–7.68 (d, 2H, J = 7.0 Hz), 4.16–4.15 (m, 1H), 3.87 (s, 3H), 3.71 (bs, 1H), 1.98–1.95 (m, 2H), 1.72–1.69 (m, 2H), 1.61–1.58 (m, 2H), 1.47–1.35 (m, 4H), 1.25 (m, 1H). Anal. Calcd. (Found) for $C_{23}H_{23}N_5O_3S$: C, 61.45 (61.46); H, 5.16 (5.18); N, 15.58 (15.60).

4.4.7. (2,4-Difluoro-benzyl)-{4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3, 4] thiadiazol-2-yl]-2-nitro-phenyl}-amine (**6h**)

IR (KBr) cm^{-1}: 3332, 3278, 3141, 2976, 1675, 1632, 1528, 1505, 1300, 1104; MS: m/z = 494 (M^+); ^{1}H NMR (DMSO-d_6): 8.86–8.83 (t, 1H, J = 6.28 Hz), 8.62 (s, 1H), 8.56 (s, 1H), 7.99–7.96 (m, 1H), 7.81–7.76 (m, 2H, Ar–H), 7.43–7.37 (m, 1H), 7.31–7.25 (m, 1H), 7.06–7.02 (m, 2H), 6.97–6.93 (m, 2H, Ar–H), 4.72 (d, 2H, J = 6.12 Hz), 3.77 (s, 3H, –methoxy H). Anal. Calcd. (Found) for $C_{24}H_{17}F_2N_5O_3S$: C, 58.41 (58.42); H3.47 (3.48); N, 14.19 (14.16).

4.4.8. 6-(4-Methoxy-phenyl)-2-(3-nitro-4-pyrrolidin-1-yl-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol (**6i**)

IR (KBr) cm^{-1}: 3135, 2932, 1657, 1654, 1572, 1380, 1383, 1120, 1088, 1171; MS: m/z = 422 (M^+); ^{1}H NMR (DMSO-d_6): 8.57 (s, 1H), 8.21 (s, 1H), 7.95–7.92 (m, 1H), 7.80–7.78 (d, 2H, J = 6.84 Hz), 7.21–7.19 (d, 1H, J = 9.12 Hz), 6.98–6.96 (d, 2H, J = 8.84 Hz), 3.7 (s, 3H), 3.23–3.22 (m, 4H), 1.95–1.92 (m, 4H). ^{13}C NMR (DMSO-d_6): 159.45, 158.75, 143.69, 130.45, 126.02, 124.73, 117.58, 114.15, 109.43, 55.18, 50.54, 25.20: Anal. Calcd. (Found) for $C_{21}H_{19}N_5O_3S$: C, 59.84 (59.85); H, 4.54 (4.55); N, 16.62 (16.60).

4.4.9. Diethyl-{4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-amine (**6j**)

IR (KBr) cm^{-1}: 3112, 2890, 1637, 1634, 1562, 1350, 1393, 1190, 1088, 1171; MS: m/z = 424 (M^+); ^{1}H NMR (DMSO-d_6): 8.58 (s, 1H), 8.20 (s, 1H), 7.98–7.95 (m, 1H), 7.81–7.79 (d, 2H, J = 8.7 Hz), 7.40–7.38 (d, 1H, J = 9.0 Hz), 6.99–6.97 (d, 2H, J = 8.84 Hz), 3.7 (s, 3H), 3.30–3.24 (m, 4H), 1.11–1.08 (m, 6H). ^{13}C NMR (DMSO-d_6): 159.09, 145.48, 145.30, 139.87, 130.47, 126.01, 124.45, 120.95, 118.71, 114.12, 109.45, 55.14, 45.64, 12.31: Anal. Calcd. (Found) for $C_{21}H_{21}N_5O_3S$: C, 59.564 (59.57); H, 5.00 (5.01); N, 16.54 (16.55).

4.4.10. Butyl-{4-[6-(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-amine (**6k**)

IR (KBr) cm^{-1}: 3321, 3112, 2890, 1637, 1634, 1562, 1350, 1393, 1190, 1088, 1171; MS: m/z = 424 (M^+); ^{1}H NMR (DMSO-d_6): 8.69 (s, 1H), 8.58–8.54 (m, 1H), 8.50 (s, 1H), 8.03–8.00 (m, 1H), 7.80–7.78

(d, 2H, $J = 8.6$ Hz), 7.27–7.25 (d, 1H, $J = 9.20$ Hz), 6.99–6.96 (d, 2H, $J = 8.7$ Hz), 3.77 (s, 3H), 3.47–3.42 (m, H), 1.66–1.59 (m, 2H), 1.43–1.36 (m, 2H), 0.94 (m, 3H). ^{13}C NMR (DMSO-d_6): 159.09, 145.48, 145.30, 139.87, 133.62, 130.47, 126.01, 125.95, 124.45, 120.95, 118.71, 114.12, 114.08, 109.45,74.31, 55.11, 30.48, 19.53, 13.57: Anal. Calcd. (Found) for $C_{21}H_{21}N_5O_3S$: C, 59.564 (59.57); H, 5.00 (5.01); N, 16.54 (16.55).

*4.4.11. (4-Fluoro-phenyl)-{4-[6(4-methoxy-phenyl)-imidazo [2,1-b] [1,3,4] thiadiazol-2-yl]-2-nitro-phenyl}-amine (**6l**)*

IR (KBr) cm^{-1}: 3165, 2962, 1687, 1644, 1542, 1350, 1373, 1170, 1064; MS: $m/z = 462$ (M^+); ^{1}H NMR (DMSO-d_6): ^{1}H NMR (DMSO-d_6): 8.86–8.83 (t, 1H, $J = 6.28$ Hz), 8.62 (s, 1H), 8.56 (s, 1H), 7.99–7.96 (m, 1H), 7.81–7.76 (m, 2H, Ar–H), 7.68–7.66 (d, 2H, $J = 7.76$ Hz, Ar–H), 7.53–7.51 (d, 2H, $J = 7.80$ Hz, Ar–H), 7.43–7.37 (m, 1H), 7.31–7.25 (m, 2H), 3.77 (s, 3H, –methoxy H). Anal. Calcd. (Found) for $C_{23}H_{16}FN_5O_3S$: C, 59.86 (59.88); H, 3.49 (3.50); N, 15.18 (15.15).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.10.056.

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