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Original article

Studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and their dihydro analogues

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Abstract

Several 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole and their dihydro analogues were synthesized from hetero aromatic acids and hetero aromatic aldehydes, respectively, by microwave-assisted dry media and conventional methods. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data elucidated the structures of all newly synthesized compounds. Synthesized compounds are studied for their antibacterial, antifungal, anti-inflammatory and analgesic activities. Some of the tested compounds showed significant pharmacological activities.

Keywords: Amino triazoles; Triazolo thiadiazoles; Dihydro triazolo thiadiazoles; Microwave synthesis; Phosphorous oxychloride

1. Introduction

1,2,4-Triazole and 1,3,4-thiadiazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities [1–5]. Various substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and their dihydro analogues are associated with diverse pharmacological activities such as antimicrobial [6], antibacterial [7], antitubercular [8], anti-inflammatory [9,10], and antifungal [11]. A triazolo thiadiazole system may be viewed as a cyclic analogue of two very important components thiosemicarbazide [12] and biguanide [13], which often display diverse biological activities.

Recently most of the reported reactions [14–17] have been carried out either in sealed vessels or in the solid phase. Microwave irradiation has been also applied to carry out organic synthesis in open vessels [18] using organic solvents such as ethanol, DMF, 1,2-dichloroethane, and *o*-dichlorobenzene as energy transfer media which absorb microwave energy efficiently through dipole rotation. Microwave-assisted reactions using dry media have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of variety of heterocyclic compounds.

Quinolines, a fused benzopyridine, pyridine and indole, fused benzopyrrole are some important nitrogen containing heterocyclic compounds having biological activities. It is reported [19] that the pyridine nucleus is associated with antitubercular, antimicrobial, antineoplastic activities and also the presence of halogen atom augments the antimicrobial properties [20] of the system. Quinoline and its derivatives are known for their antimalarial and therapeutic effects [21]. A number of quinoline derivatives are known to possess antibacterial, antifungal, hypotensive, analgesic and anti-inflammatory activities [22–25]. Applications of quinoline derivatives are fast spreading from antimalarial to almost every branch of medicinal chemistry [26,27]. Prompted by these observations, as part of our research program aimed at developing new biologically active nitrogen and sulphur containing

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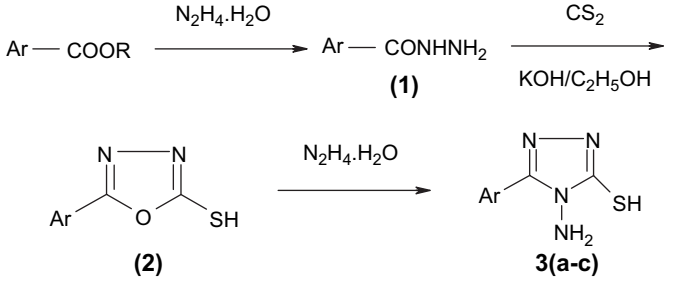
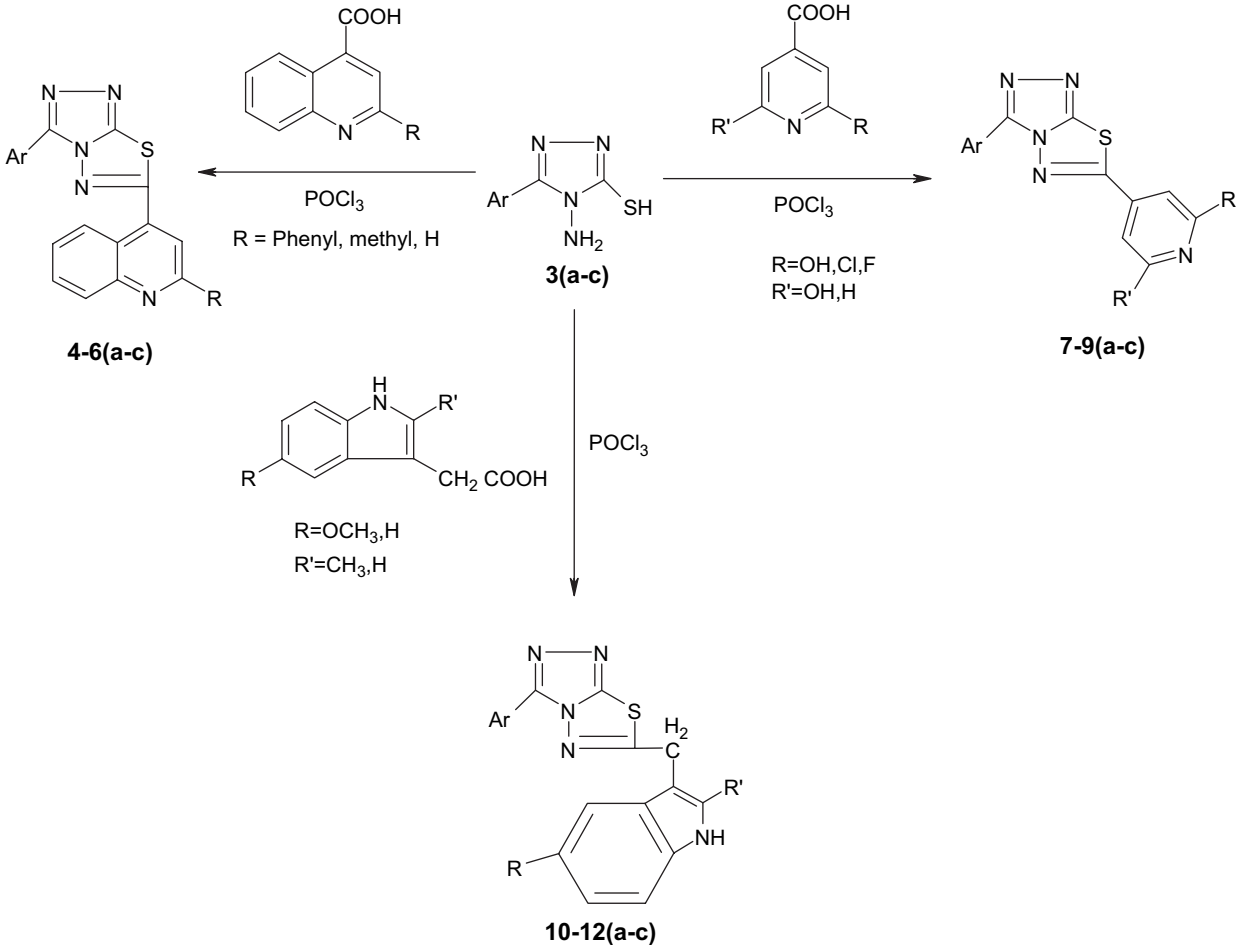
heterocycles, we report the synthesis of some new 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and their 5,6-dihydro analogues by incorporating these biologically active heterocyclic rings. The synthesis entailed the union of two biologically active nuclei, viz, triazole and thiadiazole and screening the biological activity of these fused heterocycles.



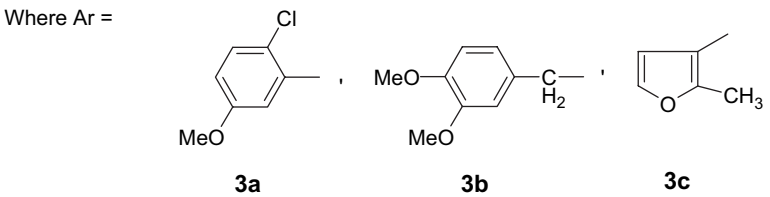
Scheme 1.

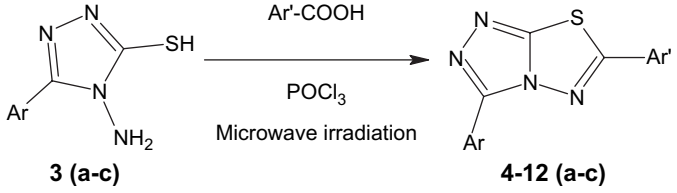
4-Amino-3-aryl/aralkyl/heteroaryl substituted-5-mercapto-1,2,4-triazole **3a–c** were prepared using the method given in Ref. [28] (Scheme 1). The structures of the intermediate triazole derivatives were based on their elemental analysis and other spectral data.

Condensation of the triazoles **3a–c** with hetero aromatic acids in the presence of phosphorous oxychloride (Schemes 2 and 3) produced a series of triazolo thiadiazoles (**4–12**); while its condensation with hetero aromatic aldehydes (Schemes 4 and 5) afforded a series of 5,6-dihydro triazolo thiadiazoles (**13–16**). The structure assigned to compounds was substantiated by their analytical and other spectral data.

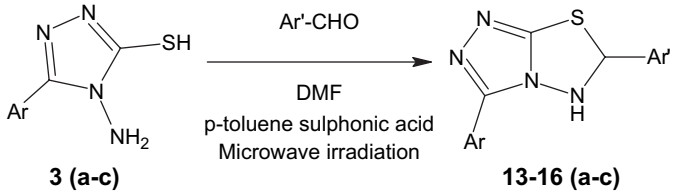


Scheme 2.





Scheme 3.



Scheme 5.

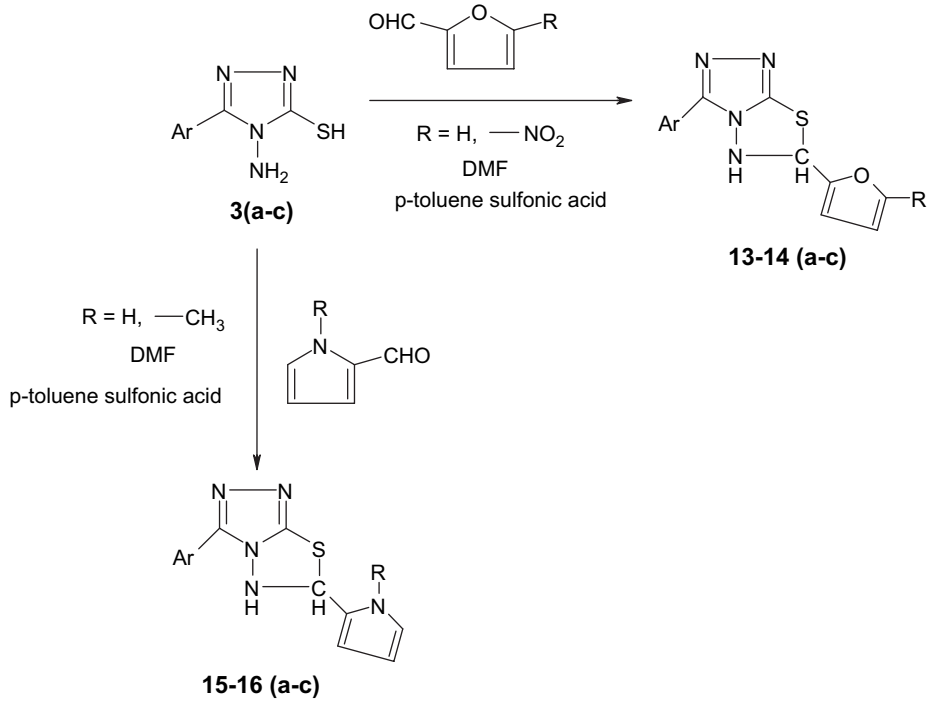
2. Results and discussion

Synthesis of 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and their 5,6-dihydro analogues under refluxing condition required 6–7 h and 10–12 h, respectively, while on solid support under microwave irradiation required shorter reaction times and higher product yields making it superior method. The IR spectra of the cyclized products showed absorption band at 3270–3290 cm^{-1} due to the NH functional group and the weak absorption band around 2580 cm^{-1} due to the SH group. This confirmed the involvement of NH_2 and SH groups of the parent amino mercapto triazole in the ring formation. An absorption band observed for all the synthesized compounds in the range of 3060–3090 cm^{-1} may be attributed to aromatic stretching vibration, while that seen at 1610–1614 cm^{-1} corresponds to C=N linkage. Thus, the formation of iminomethine functional group in the compound was indicated.

In the ^1H NMR spectra of synthesized compound, the peaks due to NH_2 and SH, which were present in the amino mercapto triazole, were absent and that further confirmed the involvement of these functional groups in the cyclization of triazole to triazolo thiadiazoles. Similarly the absence of SH proton and the down fielding of NH_2 protons (integration for one proton) in the ^1H NMR spectra established that –CHO group of the aromatic aldehydes reacted with –SH and $-NH_2$ groups of triazoles and thus converted to dihydro triazolo thiadiazoles (**13–16**). The ^1H NMR, ^{13}C NMR, mass spectra, IR and elemental analysis supported the structure of various synthesized triazolo thiadiazoles and their dihydro analogues (Tables 1–6).

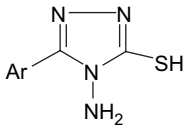
The antimicrobial results showed that some of the compounds are active against the both Gram-positive and Gram-negative bacteria. Compounds showed good inhibition of growth of the yeast-like *Candida albicans* and the fungi *Aspergillus niger*. Compounds **4–6**, **8** and **9a–c** showed the highest inhibitory effect against all the tested organisms. It can be concluded that none of the prepared compounds were superior to positive controls against various tested microbial strains, but the antibacterial and antifungal activities of some of the compounds are comparable to those of positive controls.

It was observed that the maximum antimicrobial activity was shown in the tested compounds **9a–c** having 2-flouro pyridine group at sixth position of triazolo thiadiazole system. When 2-flouro pyridine group was replaced by 2-chloro group



Scheme 4.

Table 1
Physical characterization of 5-substituted aryl-4-amino-3-mercapto-1,2,4-triazole



Compound	Ar	Melting point (m.p.) (°C)	Yield (%)	Molecular formula	Elemental analysis			
					Calculated (found) (%)			
					C	H	N	S
3a	2-Chloro-5-methoxy phenyl	230	58	$C_9H_9N_4OSCl$	42.11 (42.24)	3.53 (3.46)	21.82 (21.91)	12.49 (12.44)
3b	3,4-Dimethoxy benzyl	142	54	$C_{11}H_{14}N_4O_2S$	49.61 (49.55)	5.30 (5.35)	21.04 (21.12)	12.04 (11.98)
3c	2-Methyl-3-furanyl	158	52	$C_7H_8N_4OS$	42.84 (42.92)	4.11 (4.15)	28.55 (28.61)	16.34 (16.29)

8a–c there was a decrease in the activity while its replacement with 2-hydroxy group **7a–c** observed a sharp decrease in the antimicrobial activity. Replacement of pyridine ring by quinoline ring produced compounds with moderate activity while indole ring produced compounds with less activity.

In the quinoline substituted triazolo thiadiazole derivatives it was observed that substitution at the second position produced a decrease in the antimicrobial activity. Replacement of hydrogen at the second position by methyl produced compounds with moderate activity while its replacement by phenyl group has little role to play as far as antimicrobial activity is concerned.

None of the dihydro triazolo thiadiazoles showed good antimicrobial activity. Antimicrobial effects of the newly synthesized compounds are reported in Tables 7 and 8 as zone of inhibition against various bacterial and fungal strains, respectively.

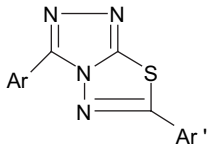
Anti-inflammatory and analgesic activity screening indicated that some of the tested compounds **10–12** (**a** and **c**) and **12b** showed good anti-inflammatory and analgesic activities. Compounds **10** and **11b** showed moderate anti-inflammatory and analgesic activities. Results revealed that maximum protection was shown in the tested compounds having indole ring at the sixth position of the triazolo thiadiazole system **10–12** (**a–c**). In the series, substitution of a methoxy group at the fifth position of indole ring produced a decrease in the anti-inflammatory and analgesic activities. Further decrease in the activities is observed with introduction of another electron releasing methyl group at the second position of 5-methoxy indole ring. Thus it was concluded that among the **10–12** (**a–c**) series, anti-inflammatory and analgesic activities decrease with the introduction of electron releasing groups.

Replacement of indole ring by other heterocyclic ring and the cyclization of triazoles to dihydro triazolo thiadiazoles produced compounds with moderate to weak anti-inflammatory and analgesic activities. Anti-inflammatory and analgesic effects of the newly synthesized compounds are reported in Tables 9 and 10, respectively.

Table 2
Spectral characterization of 5-substituted aryl-4-amino-3-mercapto-1,2,4-triazole

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	MS *m/z*
3a	3291 (NH stretching), 1613 (C=N stretching), 3130 (aromatic CH stretching), 2586 (SH), 2934, 2840 (methyl CH stretch), 1269 (asymmetric C–O–C stretching), 1021 (symmetric C–O–C stretching), 1284 (N–N=C), 1582, 1552, 1479, 1455 (C=C ring stretching)	13.92 (s, 1H, SH), 7.2, 7.5, 7.6 (3d, 3H, Ar), 5.46 (s, 2H, NH_2), 3.83 (s, 3H, OCH_3)	256 (M^+), 258 (M + 2)
3b	3286 (NH stretching), 1610 (C=N stretching); 3090 (aromatic CH stretching), 2580 (SH), 2934, 2847 (methyl CH stretch), 1264 (asymmetric C–O–C stretching), 1018 (symmetric C–O–C stretching), 1280 (N–N=C), 1588, 1548, 1486, 1455 (C=C ring stretching)	13.5 (s, 1H, SH), 6.92 (s, 1H of C-2 of Ar), 6.86, 6.74 (2d, 2H of C-5 and C-6 of Ar), 5.54 (s, 2H, NH_2), 3.78 (s, 6H, OCH_3), 3.98 (s, 2H, CH_2)	266 M^+
3c	3271 (NH stretching), 1607 (C=N stretching), 3163 (aromatic CH stretching), 1571, 1558, 1480, 1451 (C=C ring stretching), 2585 (SH), 2935, 2838 (methyl CH stretch), 1261 (asymmetric C–O–C stretching), 1037 (symmetric C–O–C stretching), 1287 (N–N=C)	13.80 (s, 1H, SH), 7.7, 7.17 (2d, 2H of furan ring), 5.6 (s, 2H, NH_2), 2.45 (s, 3H, CH_3)	196 M^+

Table 3
Physical characterization of 3,6-disubstituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole



Compound	Ar′	Melting point (m.p.) (°C)	Yield (%) (microwave)	Molecular formula	Elemental analysis			
					Calculated (found) (%)			
					C	H	N	S
4a	2-Phenyl-4-quinolinyl	198	47 (60)	$C_{25}H_{16}N_5OSCl$	63.89 (63.81)	3.43 (3.46)	14.90 (14.97)	6.82 (6.85)
4b	2-Phenyl-4-quinolinyl	186	40 (55)	$C_{27}H_{21}N_5O_2S$	67.62 (67.73)	4.41 (4.47)	14.60 (14.68)	6.69 (6.62)
4c	2-Phenyl-4-quinolinyl	212	36 (51)	$C_{23}H_{15}N_5OS$	67.47 (67.38)	3.69 (3.72)	17.10 (17.16)	7.83 (7.80)
5a	2-Methyl-4-quinolinyl	212	49 (61)	$C_{20}H_{14}N_5OSCl$	58.89 (58.82)	3.46 (3.49)	17.17 (17.24)	7.86 (7.82)
5b	2-Methyl-4-quinolinyl	208	41 (57)	$C_{22}H_{19}N_5O_2S$	63.29 (63.36)	4.59 (4.54)	16.77 (16.79)	7.68 (7.64)
5c	2-Methyl-4-quinolinyl	186	40 (54)	$C_{18}H_{13}N_5OS$	62.23 (62.15)	3.77 (3.73)	20.16 (20.27)	9.23 (9.26)
6a	4-Quinolinyl	224	48 (63)	$C_{19}H_{12}N_5OSCl$	57.94 (57.81)	3.07 (3.10)	17.78 (17.86)	8.14 (8.11)
6b	4-Quinolinyl	210	42 (56)	$C_{21}H_{17}N_5O_2S$	62.52 (62.43)	4.25 (4.30)	17.36 (17.42)	7.95 (7.91)
6c	4-Quinolinyl	200	37 (48)	$C_{17}H_{11}N_5OS$	61.25 (61.36)	3.33 (3.30)	21.01 (20.96)	9.62 (9.58)
7a	2,6-Dihydroxy-4-pyridinyl	282	49 (61)	$C_{15}H_{10}N_5O_3SCl$	47.94 (48.01)	2.68 (2.71)	18.64 (18.61)	8.53 (8.48)
7b	2,6-Dihydroxy-4-pyridinyl	262	43 (59)	$C_{17}H_{15}N_5O_4S$	52.98 (52.85)	3.92 (3.90)	18.17 (18.25)	8.32 (8.30)
7c	2,6-Dihydroxy-4-pyridinyl	270	34 (47)	$C_{13}H_9N_5O_3S$	49.52 (49.46)	2.88 (2.91)	22.21 (22.16)	10.17 (10.21)
8a	2-Chloro-4-pyridinyl	240	47 (61)	$C_{15}H_9N_5OSCl_2$	47.63 (47.54)	2.40 (2.43)	18.52 (18.58)	8.58 (8.53)
8b	2-Chloro-4-pyridinyl	224	41 (56)	$C_{17}H_{14}N_5O_2SCl$	52.65 (52.60)	3.64 (3.61)	18.06 (17.97)	8.27 (8.28)
8c	2-Chloro-4-pyridinyl	238	38 (50)	$C_{13}H_8N_5OSCl$	49.14 (49.05)	2.54 (2.59)	22.04 (22.10)	10.09 (10.05)
9a	2-Flouro-4-pyridinyl	182	51 (64)	$C_{15}H_9N_5OSCF$	49.80 (49.86)	2.51 (2.50)	19.36 (19.39)	8.86 (8.82)
9b	2-Flouro-4-pyridinyl	174	42 (57)	$C_{17}H_{14}N_5O_2SF$	54.98 (54.87)	3.80 (3.76)	18.86 (18.90)	8.63 (8.60)
9c	2-Flouro-4-pyridinyl	156	34 (50)	$C_{13}H_8N_5OSF$	51.82 (51.75)	2.68 (2.71)	23.24 (23.29)	10.64 (10.58)
10a	5-Methoxy-3-indolyl methyl	194	43 (56)	$C_{20}H_{16}N_5O_2SCl$	56.40 (56.28)	3.79 (3.83)	16.44 (16.37)	7.53 (7.49)
10b	5-Methoxy-3-indolyl methyl	172	40 (52)	$C_{22}H_{21}N_5O_3S$	60.67 (60.78)	4.86 (4.91)	16.08 (16.17)	7.36 (7.31)
10c	5-Methoxy-3-indolyl methyl	184	35 (49)	$C_{18}H_{15}N_5O_2S$	59.16 (59.24)	4.14 (4.19)	19.17 (19.25)	8.78 (8.73)
11a	5-Methoxy-2-methyl-3-indolyl methyl	206	46 (59)	$C_{21}H_{18}N_5O_2SCl$	57.33 (57.47)	4.12 (4.08)	15.92 (15.95)	7.29 (7.30)
11b	5-Methoxy-2-methyl-3-indolyl methyl	186	41 (54)	$C_{23}H_{23}N_5O_3S$	61.45 (61.52)	5.16 (5.11)	15.58 (15.67)	7.13 (7.08)
11c	5-Methoxy-2-methyl-3-indolyl methyl	180	38 (51)	$C_{19}H_{17}N_5O_2S$	60.14 (60.21)	4.52 (4.55)	18.46 (18.49)	8.45 (8.42)
12a	3-Indolyl methyl	210	44 (60)	$C_{19}H_{14}N_5OSCl$	57.65 (57.73)	3.56 (3.51)	17.69 (17.74)	8.10 (8.06)
12b	3-Indolyl methyl	194	38 (57)	$C_{21}H_{19}N_5O_2S$	62.20 (62.30)	4.72 (4.67)	17.27 (17.31)	7.91 (7.88)
12c	3-Indolyl methyl	178	35 (59)	$C_{17}H_{13}N_5OS$	60.88 (60.95)	3.91 (3.93)	20.88 (20.91)	9.56 (9.53)

3. Pharmacological activity

3.1. Anti-inflammatory activity

All the synthesized compounds were evaluated for their anti-inflammatory activity against carrageenan-induced acute paw oedema in albino rats (Wistar strain) weighing 150–200 g [29,30]. The animals were weighed and divided into control, standard, and test groups and each group contained six rats. The first group of rats was treated with 0.1 ml of 1% gum acacia suspension orally (control), second group was administered with a dose of 20 mg/kg of the suspension of phenylbutazone (standard) and the third group was treated with 20 mg/kg of the suspension of test compounds. After 30 min the animals were injected with 0.1 ml of 1% carrageenan in normal saline subcutaneously to the sub-plantar region of right hind paw. The paw volume was measured immediately ('0' h) and after 1 h, 2 h, 3 h and 4 h, respectively, by using plethysmograph. The amount of oedema in the drug-treated groups was compared in relation to the control group with the corresponding time intervals. The percentage of inhibition by the drugs was calculated by using the formula

$$\text{Percentage inhibition} = 100(1 - V_{\text{test}}/V_{\text{control}}),$$

where V_{test} = mean increase in paw volume of drug-treated group; V_{control} = mean increase in paw volume of control group.

The results were expressed as percentage inhibition of oedema over the untreated control group.

3.2. Analgesic activity

All the compounds were tested for their analgesic activity using Eddy's hot plate technique [31]. Mice (Swiss strain) of either sex weighing between 25 and 35 g were used for the experiment. In this method heat is used as a source of pain. Animals were individually placed on a hot plate maintained at constant temperature (55 °C) and the reaction of animals, such as paw licking or jump response (whichever appears first) was taken as the end point. A cut-off time of 15 s was taken as maximum analgesic response to avoid injury to the paws. The tested compounds and diclofenac sodium (standard) at a dose of 20 mg/kg body weight in 1% gum acacia were given as suspension orally to animals and observed the reaction time

Table 4
Spectral characterization of 3,6-disubstituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
4a	3080 (aromatic CH stretching), 1604 (C=N stretching), 1591, 1572, 1490, 1451 (C=C ring stretch), 2940, 2840 (methyl CH stretch), 1264 (asymmetric C–O–C stretching), 1014 (symmetric C–O–C stretch), 1280 (N–N=C)	7.18–8.6 (m, 13H, Ar-H), 3.83 (s, 3H, OCH_3)	151.29 (C3 of triazolo thiadiazole), 56.26 (C of OCH_3), 161.92, 120.71, 147.84, 129.03, 128.24, 131.87, 151.19 and 124.70 (C1, C2, C3, C4, C5, C6, C8 and C9 of quinoline ring, respectively), 140.76, 125.62, 133.76, 120.69, 160.94 and 117.48 (C1, C2, C3 C4, C5 and C6 of Ar)	470 M^+, 472 M + 2
4b	1611 (C=N stretching), 3085, 3048 (aromatic CH stretching), 1585, 1570, 1480, 1446 (C=C ring stretching), 2945, 2840 (methyl CH stretch), 1261 (asymmetric C–O–C stretching), 1021 (symmetric C–O–C stretching), 1280 (N–N=C)	6.7–8.5 (m, 13H, Ar-H), 3.78 (s, 6H, OCH_3), 4.18 (s, 2H, CH_2)	29.96 (C of CH_2), 55.48 (C of OCH_3), 160.4 (C3 of triazolo thiadiazole ring), 148.71 (C8 of triazolo thiadiazole), 136.47, 125.38, 117.27, 148.11, 149.31and 115.00 (C1, C2, C3, C4, C5 and C6 of Ar), 160.90, 120.04, 147.75, 129.23, 128.35, 131.05, 151.62 and 125.21 (C1, C2, C3, C4, C5, C6, C8 and C9 of quinoline ring)	479 M^+
4c	3095 (aromatic CH stretching), 1614 (C=N stretching), 1585, 1551, 1479, 1453 (C=C ring stretch), 2955, 2840 (methyl CH stretch), 1274 (N–N=C)	7.14–8.4 (m, 12H, Ar-H), 2.48 (s, 3H, CH_3)	13.50 (C of CH_3 in furan), 160.87 (C3 of triazolo thiadiazole ring), 147.43 (C8 of triazolo thiadiazole), 164.35, 137.41, 121.02 and 153.20 (C2, C3, C4 and C5 of Ar, respectively), 161.41, 120.12, 146.91, 128.70, 130.49, 131.29, 150.08 and 125.87 (C1, C2, C3, C4, C5, C6, C8 and C9 of quinoline ring, respectively)	409 M^+
5a	3085 (aromatic CH stretching), 1610 (C=N stretching), 1572, 1480, 1450 (C=C ring stretch), 2960, 2840 (methyl CH stretch), 1260 (asymmetric C–O–C stretching), 1020 (symmetric C–O–C stretching), 1286 (N–N=C)	7.2–8.0 (m, 8H, Ar-H), 3.85 (s, 3H, OCH_3), 2.42 (s, 2H, CH_3)	55.81 (C of OCH_3), 152.14 (C8 of triazolo thiadiazole), 140.21, 126.67, 132.10, 120.90, 160.27 and 116.81 (C1, C2, C3 C4, C5 and C6 of Ar, respectively), 24.30 (C of CH_3 in quinoline), 162.06, 121.47, 144.75, 128.06, 127.72, 131.87, 130.19, 151.80 and 124.08 (C1, C2, C3, C4, C5, C6, C7, C8 and C9 of quinoline ring)	408 M^+, 410 M + 2
5b	1608 (C=N stretching), 3080, 3040 (aromatic CH stretching), 1580, 1570, 1480, 1445 (C=C ring stretching), 2942, 2846 (methyl CH stretch), 1266 (asymmetric C–O–C stretching), 1024 (symmetric C–O–C stretching), 1286 (N–N=C)	6.8–7.9 (m, 8H, Ar-H), 3.79 (s, 6H, OCH_3), 4.14 (s, 2H, CH_2), 2.46 (s, 2H, CH_3)	29.73 (C of CH_2), 24.30 (C of CH_3 in quinoline), 162.67, 121.12, 144.91, 128.71, 127.50, 131.29, 130.08, 151.87 and 124.31 (C1, C2, C3, C4, C5, C6, C7, C8 and C9 of quinoline ring, respectively), 55.00 (C of OCH_3), 160.42 (C3 of triazolo thiadiazole ring), 147.11 (C8 of triazolo thiadiazole), 136.84, 125.42, 117.47, 148.36, 149.53 and 115.72 (C1, C2, C3, C4, C5 and C6 of Ar)	418 M^+

Table 4 (*continued*)

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
5c	3090 (aromatic CH stretching), 1610 (C=N stretching), 1580, 1561, 1484, 1445 (C=C ring stretch), 2965, 2848 (methyl CH stretch), 1276 (N–N=C)	7.1–7.9 (m, 7H, Ar-H), 2.10 (s, 3H, CH_3 of furan), 2.48 (s, 3H, CH_3 of quinoline)	13.38 (C of CH_3 in furan), 25.99 (C of CH_3 in quinoline), 161.934 (C3 of triazolo thiadiazole ring), 147.59 (C8 of triazolo thiadiazole), 166.50, 137.29, 123.086 and 153.88, (C2, C3, C4 and C5 of Ar, respectively), 161.59, 121.90, 145.60, 128.25, 127.72, 131.72, 130.12, 151.91 and 125.71 (C1, C2, C3, C4, C5, C6, C7, C8 and C9 of quinoline ring, respectively)	347 M^+
6a	3073 (aromatic CH stretching), 1607 (C=N stretching), 1592, 1570 (C=C ring stretch), 2945, 2854 (methyl CH stretch), 1267 (asymmetric C–O–C stretching), 1023 (symmetric C–O–C stretching), 1275 (N–N=C)	7.2–8.0 (m, 9H, Ar-H), 3.84 (s, 3H, OCH_3)	28.43 (C of CH_2), 55.00 (C of OCH_3), 162.42 (C3 of triazolo thiadiazole ring), 147.11 (C8 of triazolo thiadiazole), 152.84, 120.42, 144.47, 128.36, 127.53, 130.72, 150.99 and 127.38 (C1, C2, C3, C4, C5, C6, C8 and C9 of quinoline ring, respectively), 141.93, 123.59, 131.90, 118.60, 154.25 and 115.72 (C1, C2, C3 C4, C5 and C6 of Ar)	394 M^+, 396 M + 2
6b	3065, 3042 (aromatic CH stretching), 1586, 1573 (C=C ring stretching), 2960, 2854 (methyl CH stretch), 1616 (C=N stretching), 1258 (asymmetric C–O–C stretching), 1020 (symmetric C–O–C stretching), 1281 (N–N=C)	6.8–8.1 (m, 9H, Ar-H), 3.78 (s, 6H, OCH_3), 4.24 (s, 2H, CH_2)	29.25 (C of CH_2), 54.72 (C of OCH_3), 114.12 (C3 of triazolo thiadiazole ring), 147.91 (C8 of triazolo thiadiazole), 135.71, 122.50, 112.29, 145.08, 147.88 and 110.06 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 152.21, 120.02, 144.34, 128.19, 127.80, 129.50, 150.99 and 126.18 (C1, C2, C3, C4, C5, C6, C8 and C9 of quinoline ring, respectively)	403 M^+
6c	3078 (aromatic CH stretching), 1614 (C=N stretching), 1590, 1575 (C=C ring stretch), 2970, 2848 (methyl CH stretch), 1284 (N–N=C)	7.1–8.0 (m, 8H, Ar-H), 2.10 (s, 3H of furan)	13.54 (C of CH_3 in furan), 161.22 (C3 of triazolo thiadiazole ring), 147.00 (C8 of triazolo thiadiazole), 163.77, 137.20, 120.13 and 153.54, (C2, C3, C4 and C5 of Ar, respectively), 151.31, 119.99, 143.68, 127.20, 126.88, 129.77, 148.51 and 126.24 (C1, C2, C3, C4, C5, C6, C8 and C9 of quinoline ring, respectively)	333 M^+
7a	3430 (OH stretch), 3074 (aromatic CH stretch), 1612 (C=N stretch), 1590, 1541, 1480, 1455 (C=C ring stretch), 2965, 2931 (methyl CH stretch), 1230 (asymmetric C–O–C stretch), 1026 (symmetric C–O–C stretch), 1290 (N–N=C)	7.20, 7.52, 7.6 (3d, 3H of C-4, C-5, C-6 of Ar), 7.36 (s, 2H, C-3, C-5 of pyridine), 6.26 (s, 2H, OH), 3.85 (s, 3H, OCH_3)	55.37 (C of OCH_3), 155.49 (C3 of triazolo thiadiazole ring), 156.35 (C8 of triazolo thiadiazole), 140.57, 126.40, 132.81, 118.61, 160.56 and 116.83 (C1, C2, C3 C4, C5 and C6 of Ar, respectively), 159.20, 108.71, 146.63, 124.85 and 156.90 (C2, C3, C4 and C5 of pyridine ring, respectively)	375 M^+ 377 M + 2

(*continued on next page*)

Table 4 (*continued*)

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
7b	3443 (OH stretching), 3076, 3034 (aromatic CH stretching), 1607 (C=N stretching), 1590, 1538, 1478, 1448 (C=C ring stretch), 2970, 2934 (methyl CH stretch), 1262 (asymmetric C–O–C stretching), 1045 (symmetric C–O–C stretch), 1283 (N–N=C)	6.76, 6.84 (2d, 2H of C-5, C-6 in Ar), 7.0 (s, 1H of C-2 in Ar), 7.34 (s, 2H, C-3, C-5 of pyridine), 6.28 (s, 2H, OH), 3.78 (s, 6H, OCH_3), 4.22 (s, 2H, CH_2)	29.84 (C of CH_2), 55.84 (C of OCH_3), 162.11 (C3 of triazolo thiadiazole ring), 154.39 (C8 of triazolo thiadiazole), 136.47, 126.38, 119.27, 149.11 and 152.31 (C1, C2, C3 and C6, C4 and C5 of Ar, respectively), 158.25, 109.72, 148.49, 121.21 and 157.26 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	386 M^+
7c	3450 (OH stretching), 3080, 3031 (aromatic CH stretching), 1610 (C=N stretching), 1590, 1541, 1482, 1448 (C=C ring stretch), 2958, 2930 (methyl CH stretch), 1286 (N–N=C)	7.1, 7.72 (2d, 2H of furan), 7.36 (s, 2H, C-3, C-5 of pyridine), 6.3 (s, 2H, OH), 2.84 (s, 3H, CH_3)	13.73 (C of CH_3 in furan), 164.53 (C3 of triazolo thiadiazole ring), 154.47 (C8 of triazolo thiadiazole), 163.182, 136.09, 121.40 and 152.28, (C2, C3, C4 and C5 of Ar, respectively), 160.25, 106.72, 146.49, 119.21 and 154.26 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	315 M^+
8a	3065 (aromatic CH stretching), 1610 (C=N stretching), 1585, 1567, 1484, 1455 (C=C ring stretch), 2970, 2840 (methyl CH stretch), 1254 (asymmetric C–O–C stretching), 1034 (symmetric C–O–C stretch), 1275 (N–N=C)	7.22, 7.5, 7.6 (3d, 3H of C-4, C-5, C-6 in Ar), 7.76 (s, 1H, C-3 of pyridine), 7.38,7.56 (2d, 2H, C-5, C-6 of pyridine), 3.83 (s, 3H, OCH_3)	56.33 (C of OCH_3), 154.26 (C3 of triazolo thiadiazole ring), 156.48 (C8 of triazolo thiadiazole), 139.66, 125.96, 131.80, 118.32, 162.00 and 115.68 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 161.28, 126.12, 152.14, 124.99 and 156.00 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	377 M^+, 379 M + 2, 381 M + 4
8b	3084, 3048 (aromatic CH stretching), 1607 (C=N stretching), 1585, 1554, 1464, 1448 (C=C ring stretch), 2984, 2854 (methyl CH stretch), 1260 (asymmetric C–O–C stretching), 1028 (symmetric C–O–C stretching), 1284 (N–N=C)	6.76, 6.84 (2d, 2H of C-5, C-6 in Ar), 6.94 (s, 1H of C-2 in Ar), 7.8 (s, 1H, C-3′ of pyridine), 7.42, 7.56 (2d, 2H, C-5′, C-6′ of pyridine), 3.77 (s, 6H, OCH_3), 4.18 (s, 2H, CH_2)	29.50 (C of CH_2), 55.173 (C of OCH_3), 160.89 (C3 of triazolo thiadiazole ring), 147.10 (C8 of triazolo thiadiazole), 133.46, 124.79, 117.32, 145.94, 149.34 and 116.87 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 153.27, 123.83, 148.27, 121.94 and 150.55 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	387 M^+, 389 M + 2
8c	3080, 3038 (aromatic CH stretching), 1614 (C=N stretching), 1587, 1550, 1482, 1448 (C=C ring stretch), 2958, 2854 (methyl CH stretch), 1276 (N–N=C)	7.86 (s, 1H of C-3 of pyridine), 7.38, 7.6 (2d, 2H, C-5′, C-6′ of pyridine), 7.14, 7.70 (2d, 2H of furan), 2.0 (s, 3H, CH_3 of furan)	13.57 (C of CH_3 in furan), 164.19 (C3 of triazolo thiadiazole ring), 155.10 (C8 of triazolo thiadiazole), 164.10, 136.10, 120.39 and 154.01 (C2, C3, C4 and C5 of furan, respectively), 159.41, 134.14, 151.97, 128.04 and 157.36 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	317 M^+, 319 M + 2

Table 4 (*continued*)

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
9a	3082 (aromatic CH stretching), 1618 (C=N stretching), 1580, 1574 (C=C ring stretch), 2964, 2846 (methyl CH stretch), 1258 (asymmetric C–O–C stretching), 1028 (symmetric C–O–C stretching), 1280 (N–N=C)	7.16, 7.44, 7.6 (3d, 3H, C-4, C-5, C-6 of Ar), 7.86 (s, 1H of C-3 of pyridine), 7.32, 7.52 (2d, 2H of C-5, C-6 of pyridine), 3.85 (s, 3H, OCH_3)	56.38 (C of OCH_3), 151.72 (C3 of triazolo thiadiazole ring), 151.22 (C8 of triazolo thiadiazole), 139.65, 125.70, 131.12, 118.91, 163.71 and 115.50 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 167.29, 110.08, 152.87, 120.50 and 150.73 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	362 M^+, 364 M + 2
9b	3090 (aromatic CH stretching), 1617 (C=N stretching), 1575, 1560 (C=C ring stretch), 2954, 2837 (methyl CH stretch), 1260 (asymmetric C–O–C stretching), 1024 (symmetric C–O–C stretching), 1284 (N–N=C)	6.74, 6.88 (2d, 2H of C-5, C-6 in Ar), 6.98 (s, 1H of C-2 in Ar), 7.80 (s, 1H of C-3 of pyridine), 7.44, 7.62 (2d, 2H of C-5, C-6 of pyridine), 3.79 (s, 6H, OCH_3), 4.22 (s, 2H, CH_2)	29.18 (C of CH_2), 56.72 (C of OCH_3), 160.30 (C3 of triazolo thiadiazole ring), 147.51 (C8 of triazolo thiadiazole), 131.27, 123.83, 116.27, 144.83, 147.27 and 115.94 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 166.55, 110.38, 150.61, 121.13 and 149.93 (C2, C3, C4, C5 and C6 of pyridine ring, respectively)	372 M^+
9c	3080, 3038 (aromatic CH stretch), 1614 (C=N stretching), 1587, 1550, 1482, 1448 (C=C ring stretch), 2958, 2854 (methyl CH stretch), 1276 (N–N=C)	7.80 (s, 1H of C-3 of pyridine), 7.48, 7.60 (2d, 2H, C-5, C-6 of pyridine), 7.10, 7.70 (2d, 2H of furan), 2.1 (s, 3H, CH_3 of furan)	13.51 (C of CH_3 in furan), 161.45 (C3 of triazolo thiadiazole ring), 156.61 (C8 of triazolo thiadiazole), 163.92, 135.47, 119.76, 154.36, (C2, C3, C4, C5 of furan), 171.18, 116.26, 153.16, 125.93, 155.41 (C2, C3, C4, C5 and C6 of pyridine ring)	301 M^+
10a	3084 (aromatic CH stretching), 1614 (C=N stretching), 1587, 1565 (C=C ring stretch), 2980, 2849 (methyl CH stretch), 1265 (asymmetric C–O–C stretching), 1018 (symmetric C–O–C stretching), 1282 (N–N=C)	7.22, 7.5, 7.6 (3d, 3H of C-4, C-5, C-6 of Ar), 7.4 (s, 1H of C-4′ of indole), 7.66, 7.7 (2d, 2H of C-6′, C-7′ of indole), 7.1 (s, 1H of C-2′ of indole), 3.82–3.84 (2s, 6H, of OCH_3), 4.68 (s, 2H, CH_2), 9.8 (s, 1H, NH of pyrrole)	28.315 (C of CH_2), 154.385 (C3 of triazolo thiadiazole ring), 156.708 (C8 of triazolo thiadiazole), 55.945 (C of OCH_3), 126.327, 115.190, 139.75, 109.49, 163.59, 107.851, 116.271 and 134.485 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively), 147.82, 127.105, 133.49, 121.406, 167.31 and 113.217 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	426 M^+, 428 M + 2
10b	3070 (aromatic CH stretching), 1624 (C=N stretching), 1588, 1546 (C=C ring stretch), 2956, 2864 (methyl CH stretch), 1260 (asymmetric C–O–C stretching), 1021 (symmetric C–O–C stretching), 1285 (N–N=C)	9.74 (s, 1H, NH), 6.76, 6.84 (2d, 2H of C-5, C-6 of Ar), 6.94 (s, 1H of C-2′ of Ar), 7.4 (s, 1H of C-4′ of indole), 7.6, 7.72 (2d, 2H of C-6′, C-7′ of indole), 7.12 (s, 1H of C-2 of indole), 4.24 (s, 2H, CH_2 of Ar), 3.78 (s, 6H, OCH_3 in Ar), 3.84 (s, 3H, OCH_3 in indole), 4.60 (s, 2H, CH_2 of indole)	29.34 and 28.80 (C of two CH_2), 54.69 (C of OCH_3), 124.58, 115.10, 134.73, 126.85, 128.04, 123.61, 115.94 and 141.60 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively), 139.56, 127.47, 120.39, 144.14, 149.25, 116.31 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	435 M^+

(*continued on next page*)

Table 4 (*continued*)

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
10c	3063 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1549, 1479, 1452 (C=C ring stretch), 2964, 2838 (methyl CH stretch), 1267 (asymmetric C–O–C stretching), 1029 (symmetric C–O–C stretching), 1280 (N–N=C)	7.2, 7.8 (2d, 2H of C-4, C-5 of Ar), 7.44 (s, 1H of C-4′ of indole), 7.62, 7.7 (2d, 2H of C-6′, C-7′ of indole), 7.06 (s, 1H of C-2′ of indole), 3.83 (s, 3H, of OCH_3 in indole), 4.62 (s, 2H, CH_2 of indole), 9.8 (s, 1H, NH), 1.98 (s, 3H, CH_3)	13.73 (C of CH_3) 28.65 (C of CH_2), 54.63 (C of OCH_3), 126.56, 117.16, 136.24, 109.10, 159.031, 108.47, 116.25 and 131.49 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively), 157.48, 127.25, 114.37 and 150.71 (C2, C3, C4 and C5 of furan, respectively)	365 M^+
11a	3075 (aromatic CH stretching), 1610 (C=N stretching), 1587, 1565 (C=C ring stretch), 2980, 2849 (methyl CH stretch), 1265 (asymmetric C–O–C stretching), 1018 (symmetric C–O–C stretching), 1282 (N–N=C)	7.2, 7.5, 7.64 (3d, 3H of C-4, C-5, C-6 of Ar), 7.4 (s, 1H of C-4′ of indole), 7.62, 7.74 (2d, 2H of C-6′, C-7′ of indole), 3.82–3.84 (2s, 6H, of OCH_3), 4.62 (s, 2H, CH_2 of indole), 9.68 (s, 1H, NH of pyrrole), 2.72 (s, 3H, CH_3)	28.42 (C of CH_2), 13.93 (C of CH_3), 54.38 (C of OCH_3), 139.91, 127.60, 136.51, 121.57, 163.27 and 115.90 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 126.32, 115.19, 139.75, 109.49, 163.59, 107.85, 116.27 and 134.48 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively)	440 M^+, 442 M + 2
11b	3082 (aromatic CH stretching), 1610 (C=N stretching), 1588, 1561 (C=C ring stretch), 2956, 2856 (methyl CH stretch), 1268 (asymmetric C–O–C stretching), 1024 (symmetric C–O–C stretching), 1286 (N–N=C)	9.74 (s, 1H, NH of pyrrole), 6.72, 6.84 (2d, 2H of C-5, C-6 in Ar), 6.96 (s, 1H of C-2 in Ar), 7.44 (s, 1H of C-4′ of indole), 7.56, 7.68 (2d, 2H of C-6′, C-7′ of indole), 4.32 (s, 2H, CH_2 of Ar), 3.77 (s, 6H, OCH_3 in Ar), 3.83 (s, 3H, OCH_3 in indole), 4.60 (s, 2H, CH_2 of indole), 2.8 (s, 3H, CH_3)	29.21 and 28.77 (C of two CH_2), 54.50 and 54.16 (C of two OCH_3), 13.30 (C of CH_3), 139.91, 127.60, 136.51, 148.70, 149.05 and 117.38 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 144.53, 117.35, 137.19, 109.30, 160.94, 106.73, 114.20 and 132.15 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively)	450 M^+
11c	3068 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1554 (C=C ring stretch), 2943, 2860 (methyl CH stretch), 1254 (asymmetric C–O–C stretching), 1023 (symmetric C–O–C stretching), 1288 (N–N=C)	7.16, 7.8 (2d, 2H of furan), 7.36 (s, 1H of C-4′ in indole), 7.56, 7.66 (2d, 2H of C-6′, C-7′ in indole), 3.85 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2 of indole), 9.74 (s, 1H, NH), 1.98 (s, 3H, CH_3), 2.8 (s, 3H, CH_3)	13.49 and 14.01 (C of two CH_3), 28.06 (C of CH_2), 54.58 (C of OCH_3), 143.17, 117.44, 136.53, 109.13, 161.27, 108.25, 114.14 and 132.06 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively), 154.35, 127.11, 114.50 and 149.31 (C2, C3, C4 and C5 of furan, respectively)	379 M^+
12a	3092 (aromatic CH stretching), 1623 (C=N stretching), 1583, 1545 (C=C ring stretch), 2980, 2855 (methyl CH stretch), 1267 (asymmetric C–O–C stretching), 1018 (symmetric C–O–C stretching), 1282 (N–N=C)	7.18, 7.48, 7.6 (3d, 3H of C-4, C-5, C-6 of Ar), 7.36 (s, 1H of C-4′ in indole), 7.7 (d, 1H of C-7′ in indole), 7.5–7.66 (m, 2H, C-5′, C-6′ of indole), 7.06 (s, 1H of C-2′ of indole), 3.81 (s, 3H, of OCH_3), 4.68 (s, 2H, CH_2 of indole), 9.84 (s, 1H, NH)	28.506 (C of CH_2), 56.47 (C of OCH_3), 145.19, 127.53, 136.71, 119.10, 167.49 and 114.23 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 126.29, 115.37, 134.10, 121.35, 123.07, 120.21, 112.29 and 140.53 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively)	396 M^+

Table 4 (*continued*)

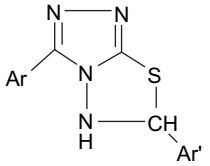
Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
12b	3071 (aromatic CH stretching), 1608 (C=N stretching), 1574, 1540 (C=C ring stretch), 2956, 2834 (methyl CH stretch), 1261 (asymmetric C–O–C stretching), 1019 (symmetric C–O–C stretching), 1280 (N–N=C)	6.78, 6.86 (2d, 2H of C-5, C-6 in Ar), 6.94 (s, 1H of C-2 in Ar), 7.44 (s, 1H of C-4′ in indole), 7.5–7.64 (m, C-5′, C-6′ of indole), 7.7 (d, 1H of C-7′ in indole), 7.12 (s, 1H of C-2 of pyrrole), 4.24 (s, 2H, CH_2 of Ar), 3.77 (s, 6H, OCH_3 in Ar), 4.60 (s, 2H, CH_2 of indole), 9.74 (s, 1H, NH)	29.47 and 28.65 (C of two CH_2), 54.38 (C of OCH_3), 126.57, 117.14, 136.82, 121.07, 123.39, 120.01, 116.64 and 142.09 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively), 138.21, 128.30, 121.07, 149.49, 151.52 and 117.13 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	406 M^+
12c	3060 (aromatic CH stretching), 1616 (C=N stretching), 1571, 1549 (C=C ring stretch), 2952, 2839 (methyl CH stretch), 1271 (N–N=C)	7.16, 7.8 (2d, 2H of C-4, C-5 of Ar), 7.38 (s, 1H of C-4′ in indole), 7.7 (d, H of C-7′ in indole), 7.5–7.64 (m, C-5′, C-6′ of indole), 7.08 (s, 1H of C-2′ of indole), 4.64 (s, 2H, CH_2 of indole), 9.82 (s, 1H, NH), 1.96 (s, 3H, CH_3)	13.73 (C of CH_3) 28.72 (C of CH_2), 126.56, 117.16, 136.24, 109.10, 159.03, 108.47, 116.25 and 131.49 (C2, C3, C4, C5, C6, C7, C8 and C9 of indole ring, respectively), 157.48, 127.25, 114.37 and 150.71 (C2, C3, C4 and C5 of furan, respectively)	335 M^+

of animals on the hot plate at 15, 30, 60, 90 and 120 min after the compound administration. Percentage analgesic activity shown by the tested compounds is recorded in Table 10.

3.3. Antibacterial and antifungal activities

Applying the agar plate diffusion technique [32] all of the newly synthesized compounds were screened in vitro for antibacterial activity against *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (Gram-negative), *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive) at 10 μg/ml, 20 μg/ml, 30 μg/ml concentrations, respectively. Under identical conditions, the positive control antibiotics amikacin at 30 μg/ml showed zone of inhibition 23–24 mm for Gram-negative organism and vancomycin at 30 μg/ml showed zone of inhibition 23 mm for Gram-positive organism. Similarly, the antifungal screening of the compounds was carried out in vitro by paper disc method against two fungi *A. niger* and *C. albicans* by using griseofulvin (30 μg/ml) as the positive control, which showed 23 mm and 25 mm, respectively, as the zone of inhibition.

Table 5
Physical characterization of 3,6-disubstituted-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole



Compound	Ar′	Melting point (m.p.) (°C)	Yield (%) (microwave)	Molecular formula	Elemental analysis			
					Calculated (found) (%)			
					C	H	N	S
13a	2-Furanyl	172	45 (59)	$C_{13}H_{11}N_4O_2SCl$	50.23 (50.30)	3.31 (3.34)	16.74 (16.80)	9.58 (9.59)
13b	2-Furanyl	160	42 (53)	$C_{16}H_{16}N_4O_3S$	55.80 (55.87)	4.68 (4.68)	16.27 (16.32)	9.31 (9.29)
13c	2-Furanyl	180	38 (53)	$C_{12}H_{10}N_4O_2S$	52.54 (52.46)	3.67 (3.69)	20.43 (20.41)	11.69 (11.65)
14a	5-Nitro-2-furanyl	224	50 (65)	$C_{14}H_{10}N_5O_4SCl$	44.28 (44.34)	2.65 (2.67)	18.44 (18.51)	8.44 (8.42)
14b	5-Nitro-2-furanyl	218	41 (56)	$C_{16}H_{15}N_5O_5S$	49.35 (49.43)	3.88 (3.90)	17.99 (18.04)	8.23 (8.26)
14c	5-Nitro-2-furanyl	214	35 (52)	$C_{12}H_9N_5O_4S$	45.14 (45.08)	2.84 (2.86)	21.93 (21.89)	10.04 (10.01)
15a	Pyrol-2-yl	176	47 (62)	$C_{14}H_{12}N_5OSCl$	50.38 (50.47)	3.62 (3.60)	20.98 (21.07)	9.61 (9.57)
15b	Pyrol-2-yl	162	43 (58)	$C_{16}H_{17}N_5O_2S$	55.96 (56.06)	4.99 (5.02)	20.39 (20.45)	9.34 (9.30)
15c	Pyrol-2-yl	180	40 (57)	$C_{12}H_{11}N_5OS$	52.73 (52.67)	4.06 (4.04)	25.62 (25.68)	11.73 (11.69)
16a	*N*-Methyl-pyrol-2-yl	184	47 (60)	$C_{20}H_{16}N_5OSCl$	58.60 (58.67)	3.93 (3.96)	17.09 (17.13)	7.82 (7.85)
16b	*N*-Methyl-pyrol-2-yl	174	40 (57)	$C_{22}H_{21}N_5O_2S$	62.99 (63.06)	5.05 (5.01)	16.69 (16.73)	7.64 (7.66)
16c	*N*-Methyl-pyrol-2-yl	162	36 (54)	$C_{18}H_{15}N_5OS$	61.87 (61.79)	4.33 (4.34)	20.04 (19.92)	9.18 (9.20)

Table 6
Spectral characterization of 3,6-disubstituted-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
13a	3370 (NH stretching), 3056 (aromatic CH stretching), 1618 (C=N stretching), 1580, 1535 (C=C ring stretch), 1264 (asymmetric C–O–C stretching), 1017 (symmetric C–O–C stretching)	7.14, 7.5, 7.60 (3d, 3H of C-4, C-5, C-6 of Ar), 6.84 (d, 1H, C-3′ of Ar), 7.24 (m, 1H of C-4′ of furan), 7.78 (d, 1H C-5′ of furan), 5.56 (s, 1H, CH, in –CH–NH), 6.20 (s, 1H of NH in –NH–CH), 3.83 (s, 3H, OCH_3)	56.23 (C of OCH_3), 90.74 (C6 of triazolo thiadiazole), 161.39, 113.24, 125.37 and 153.14 (C2, C3, C4 and C5 of furan ring, respectively), 144.80, 127.18, 137.21, 118.57, 165.64 and 116.38 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	335 M^+, 337 M + 2
13b	3350 (NH stretching), 3076 (aromatic CH stretching), 1617 (C=N stretching), 1576, 1552, 1480 (C=C ring stretch), 1262 (asymmetric C–O–C stretching), 1020 (symmetric C–O–C stretching)	6.80, 6.92 (2d, 2H, C-5, C-6 of Ar), 7.0 (s, 1H, C-2 of Ar), 6.96 (d, 1H, C-3′ of furan), 7.24 (m, 1H, C-4′ of furan), 7.76 (d, 1H, C-5′ of furan), 5.60 (s, 1H, CH, in CH–NH), 6.22 (s, 1H of NH in NH–CH), 3.83 (s, 6H, OCH_3), 4.28 (s, 2H, CH_2)	93.15 (C6 of triazolo thiadiazole), 159.96, 112.18, 125.32 and 153.63 (C2, C3, C4 and C5 of furan ring, respectively), 37.26 (C of CH_2), 54.31 (C of OCH_3), 140.62, 127.53, 118.68, 148.81, 152.07 and 116.39 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	344 M^+
13c	3328 (NH stretching), 3080 (aromatic CH stretching), 1620 (C=N stretching), 1580, 1552, 1484 (C=C ring stretch), 1258 (asymmetric C–O–C stretching), 1023 (symmetric C–O–C stretching)	7.1, 7.64 (2d, 2H, C-4 and C-5 of Ar), 6.90 (d, 1H, C-3′ of furan at C-6), 7.20 (m, 1H, C-4′ of furan at C-6), 7.76 (d, 1H C-5′ of furan at C-6), 5.58 (s, 1H, CH, –CH–NH), 6.16 (s, 1H, NH in –NH–CH), 1.92 (s, 3H, CH_3 of Ar)	14.28 (C of CH_3), 155.29, 131.48, 117.51 and 153.35 (C2, C3, C4 and C5 of Ar, respectively), 90.74 (C6 of triazolo thiadiazole), 161.29, 113.75, 126.61 and 153.48 (C2, C3, C4 and C5 of furan ring, respectively)	274 M^+
14a	3338 (NH stretch), 3086 (aromatic CH stretch), 1619 (C=N stretch), 1590, 1558 (C=C ring stretch), 1265 (asymmetric C–O–C stretch), 1017 (symmetric C–O–C stretch), 1527 (asymmetric NO_2 stretch), 1347 (symmetric NO_2 stretch)	7.16, 7.56, 7.62 (3d, 3H of C-4, C-5, C-6 of Ar), 7.36 (d, 1H, C-3′ of furan), 7.90 (d, 1H of C-4′ of furan), 5.58 (s, 1H, CH of –CH–NH), 6.24 (s, 1H of NH in –NH–CH), 3.83 (s, 3H, OCH_3)	55.47 (C of OCH_3), 92.38 (C6 of triazolo thiadiazole), 163.38, 115.62, 131.07 and 159.15 (C2, C3, C4 and C5 of furan ring, respectively), 146.26, 127.10, 139.47, 120.50, 166.02 and 118.13 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	380 M^+, 382 M + 2
14b	3350 (NH stretch), 3079 (aromatic CH stretch), 1615 (C=N stretch), 1584, 1547, 1492 (C=C ring stretch), 1258 (asymmetric C–O–C stretch), 1021 (symmetric C–O–C stretch), 1519 (asymmetric NO_2 stretch), 1348 (symmetric NO_2 stretch)	6.82, 6.90 (2d, 2H of C-5, C-6 in Ar), 7.0 (s, 1H of C-2 in Ar), 7.40 (d, 1H, C-3′ of furan), 7.94 (d, 1H of C-4′ of furan), 5.58 (s, 1H, CH in –CH–NH), 6.16 (s, 1H of NH in –NH–CH), 3.79 (s, 6H, OCH_3), 4.32 (s, 2H, CH_2)	94.27 (C6 of triazolo thiadiazole), 166.31, 117.49, 130.04 and 159.24 (C2, C3, C4 and C5 of furan ring, respectively), 35.19 (C of CH_2), 54.72 (C of OCH_3), 143.58, 126.96, 120.47, 151.17, 152.90 and 116.39 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	389 M^+
14c	3345 (NH stretching), 3084 (aromatic CH stretching), 1620 (C=N stretching), 1580, 1542, 1490 (C=C ring stretch), 1530 (asymmetric NO_2 stretch), 1340 (symmetric NO_2 stretch)	7.1, 7.72 (2d, 2H, C-4 and C-5 of Ar), 7.42 (d, 1H, C-3′ of furan), 7.92 (d, 1H of C-4′ of furan), 5.60 (s, 1H, CH in –CH–NH), 6.26 (s, 1H of NH in –NH–CH), 1.96 (s, 3H, CH_3 of Ar)	14.28 (C of CH_3), 155.29, 131.48, 117.51 and 153.35 (C2, C3, C4 and C5 of Ar, respectively), 93.38 (C6 of triazolo thiadiazole), 165.74, 115.23, 128.59 and 159.71 (C2, C3, C4 and C5 of furan ring, respectively)	319 M^+
15a	3352 (NH stretching), 3070 (aromatic CH stretching), 1619 (C=N stretching), 1586, 1554 (C=C ring stretch), 1263 (asymmetric C–O–C stretching), 1019 (symmetric C–O–C stretching)	7.14, 7.52, 7.64 (3d, 3H of C-4, C-5, C-6 of Ar), 6.42 (d, 1H, C-3′ of pyrrole), 6.60 (m, 1H, C-4′ of pyrrole), 7.04 (d, 1H, C-5′ of pyrrole), 5.60 (s, 1H, CH in CH–NH), 6.26 (s, 1H of NH in –NH–CH), 9.8 (s, 1H, NH of pyrrole), 3.82 (s, 3H, OCH_3)	56.31 (C of OCH_3), 94.27 (C6 of triazolo thiadiazole), 144.35, 121.14, 120.74 and 130.06 (C2, C3, C4 and C5 of pyrrole ring, respectively), 147.10, 126.83, 139.05, 120.17, 165.68 and 118.24 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	334 M^+, 336 M + 2

Table 6 (*continued*)

Compound	IR (KBr) ν (cm^{-1})	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	MS *m/z*
15b	3365 (NH stretching), 3083 (aromatic CH stretching), 1617 (C=N stretching), 1586, 1550, 1470 (C=C ring stretch), 1257 (asymmetric C–O–C stretching), 1021 (symmetric C–O–C stretching)	6.82, 6.90 (2d, 2H of C-5, C-6 in Ar), 7.0 (s, 1H of C-2 in Ar), 6.46 (d, 1H, C-3′ of pyrrole), 6.60 (m, 1H of C-4′ of pyrrole), 7.06 (d, 1H of C-5′ of pyrrole), 5.68 (s, 1H, CH in –CH–NH), 6.26 (s, 1H of NH in –NH–CH), 9.6 (s, 1H, NH of pyrrole), 3.78 (s, 6H, OCH_3), 4.32 (s, 2H, CH_2)	94.17 (C6 of triazolo thiadiazole), 145.30, 128.14, 122.69, 154.58, 157.17 and 118.30 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 144.51, 120.42, 119.80 and 131.37 (C2, C3, C4 and C5 of pyrrole ring, respectively), 37.60 (C of CH_2), 55.43 (C of OCH_3)	343 M^+
15c	3348 (NH stretching), 3076 (aromatic CH stretching), 1615 (C=N stretching), 1580, 1568, 1490 (C=C ring stretch), 1259 (asymmetric C–O–C stretching), 1024 (symmetric C–O–C stretching)	7.1, 7.68 (2d, 2H, C-4 and C-5 of Ar), 6.59 (m, 1H of C-4′ of pyrrole), 7.06 (d, 1H of C-5′ of pyrrole), 5.64 (s, 1H, CH in –CH–NH), 6.18 (s, 1H of NH in –NH–CH), 9.8 (s, 1H, NH of pyrrole), 1.94 (s, 3H, CH_3 of Ar)	13.47 (C of CH_3), 157.10, 131.71, 118.15 and 153.29 (C2, C3, C4 and C5 of Ar), 94.79 (C6 of triazolo thiadiazole), 144.47, 121.03, 120.95 and 130.24 (C2, C3, C4 and C5 of pyrrole ring, respectively)	273 M^+
16a	3364 (NH stretching), 3062 (aromatic CH stretching), 1610 (C=N stretching), 1580, 1553 (C=C ring stretch), 1266 (asymmetric C–O–C stretching), 1021 (symmetric C–O–C stretching), 2963, 2847 (methyl CH stretch)	7.12, 7.48, 7.60 (3d, 3H of C-4, C-5, C-6 of Ar), 6.88 (d, 1H, C-5′ of pyrrole), 6.56 (m, 1H, C-4′ of pyrrole), 6.40 (d, 1H, C-3′ of pyrrole), 5.62 (s, 1H, of –CH–NH), 6.20 (s, 1H of NH in –NH–CH), 3.56 (s, 3H, N–CH_3), 3.84 (s, 3H, OCH_3)	47.61 (C of CH_3 in pyrrole), 87.10 (C6 of triazolo thiadiazole), 148.36, 126.72, 138.68, 119.55, 165.40 and 118.21 (C1, C2, C3, C4, C5 and C6 of Ar, respectively), 56.31 (C of OCH_3), 149.38, 121.82, 120.90 and 137.53 (C2, C3, C4 and C5 of pyrrole ring, respectively)	409 M^+, 411 M + 2
16b	3364 (NH stretching), 3058 (aromatic CH stretching), 1615 (C=N stretching), 1589, 1565, 1480 (C=C ring stretch), 1258 (asymmetric C–O–C stretching), 1025 (symmetric C–O–C stretching), 2958, 2849 (methyl CH stretch)	6.80 (d, 1H of C-5 of Ar), 7.0 (s, 1H of C-2 in Ar), 6.9 (m, 2H, C-6 of Ar and C-5′ of pyrrole), 6.52 (m, 1H, C-4′ of pyrrole), 6.38 (d, 1H, C-3′ of pyrrole), 5.52 (s, 1H, of –CH–NH), 6.26 (s, 1H of NH in –NH–CH), 3.64 (s, 3H of N–CH_3), 3.79 (s, 6H, OCH_3), 4.34 (s, 2H, CH_2)	48.63 (C of CH_3 in pyrrole), 86.57 (C6 of triazolo thiadiazole), 57.15 (C of OCH_3), 148.36, 121.75, 120.33 and 137.07 (C2, C3, C4 and C5 of pyrrole ring, respectively), 34.13 (C of CH_2), 145.05, 128.27, 123.14, 154.71, 158.38 and 118.16 (C1, C2, C3, C4, C5 and C6 of Ar, respectively)	419 M^+
16c	3345 (NH stretching), 3072 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1549, 1480 (C=C ring stretch), 1264 (asymmetric C–O–C stretching), 1022 (symmetric C–O–C stretching), 2965, 2850 (methyl CH stretch)	7.14, 7.7 (2d, 2H, C-4 and C-5 of Ar), 7.00 (d, 1H, C-5′ of pyrrole), 6.82 (m, 1H, C-4′ of pyrrole), 6.64 (d, 1H, C-3′ of pyrrole), 5.50 (s, 1H, of CH–NH), 6.16 (s, 1H of NH of NH–CH), 3.60 (s, 3H of N–CH_3), 1.92 (s, 3H, CH_3 of Ar)	14.18 (C of CH_3), 48.39 (C of CH_3 in pyrrole), 85.38 (C6 of triazolo thiadiazole), 156.29, 131.52, 117.36 and 153.20 (C2, C3, C4 and C5 of Ar, respectively), 149.11, 121.75, 121.19 and 137.40 (C2, C3, C4 and C5 of pyrrole, respectively)	349 M^+

4. Experimental section

Thin layer chromatography was used to reach the completion of the reaction and purity of the compounds synthesized. Melting points were determined in open glass capillary tubes using thiels tube containing liquid paraffin and were uncorrected. IR spectra were obtained in KBr discs on a Shimadzu-8400 FTIR spectrophotometer, ^1H NMR spectra were recorded on Brucker spectrophotometer (400 MHz) in DMSO-d_6/$CDCl_3$ using TMS as an internal standard, mass spectra were recorded on Finnigan MAT 8230 mass spectrophotometer, ^{13}C NMR spectra were recorded on Brucker spectrophotometer (100 MHz) in DMSO-d_6/$CDCl_3$ and elemental analyses were performed using Thermo Finnigan FLASH EA 1112 CHNS analyser. The purity of the compounds was checked on silica gel-G coated plates by using ethyl acetate and petroleum ether (1:1) as the eluent and observed under UV light. All the synthesized compounds gave satisfactory elemental analyses.

5. Materials and methods

*5.1. General procedure for the preparation of aryl hydrazide (**1**)*

To the methyl/ethyl esters of substituted aromatic acids (0.1 M), hydrazine hydrate (0.1 M) was added and refluxed the solution for 30 min. Ethanol (20 ml) was added to the

Table 7
Antifungal activities of compounds[a] (**3–16**)

Compound	*Candida albicans*			*Aspergillus niger*		
	10 (μg/ml) ± SD[b]	20 (μg/ml) ± SD[b]	30 (μg/ml) ± SD[b]	10 (μg/ml) ± SD[b]	20 (μg/ml) ± SD[b]	30 (μg/ml) ± SD[b]
3a	2.33 ± 0.58	5.18 ± 1.53	9.79 ± 0.47	2.59 ± 0.58	5.02 ± 0.53	11.04 ± 0.61
3b	2.76 ± 0.58	5.14 ± 1.16	11.00 ± 1.00	2.67 ± 0.53	4.92 ± 0.58	10.67 ± 1.53
3c	3.00 ± 0.00	6.82 ± 1.73	12.44 ± 1.53	3.27 ± 0.58	6.94 ± 0.61	13.48 ± 0.58
4a	5.64 ± 1.16	12.84 ± 1.73	18.78 ± 1.53	6.04 ± 0.58	11.63 ± 0.58	17.58 ± 1.16
4b	5.82 ± 0.58	11.37 ± 0.58	17.95 ± 1.73	6.14 ± 0.58	11.54 ± 1.16	16.72 ± 1.53
4c	6.27 ± 0.58	14.84 ± 1.16	19.36 ± 1.53	5.92 ± 0.58	11.00 ± 2.00	17.67 ± 0.58
5a	6.18 ± 1.16	13.82 ± 0.58	18.75 ± 0.61	5.62 ± 0.47	12.62 ± 0.58	18.54 ± 0.27
5b	5.48 ± 0.58	12.00 ± 1.00	17.48 ± 1.53	6.25 ± 0.58	13.00 ± 1.00	16.72 ± 0.27
5c	5.84 ± 0.53	12.62 ± 0.58	19.00 ± 1.00	6.00 ± 0.00	13.46 ± 0.58	17.42 ± 1.16
6a	6.48 ± 0.58	13.92 ± 1.73	18.00 ± 1.00	6.40 ± 0.61	12.85 ± 0.58	19.10 ± 1.53
6b	6.14 ± 0.58	13.66 ± 0.47	17.82 ± 0.27	6.32 ± 0.61	13.00 ± 2.00	18.00 ± 0.00
6c	5.78 ± 0.58	11.00 ± 1.00	19.24 ± 1.53	6.14 ± 0.58	12.00 ± 1.00	19.62 ± 0.58
7a	4.14 ± 0.58	7.15 ± 0.58	15.00 ± 1.00	4.82 ± 0.58	8.06 ± 0.47	13.62 ± 1.16
7b	3.82 ± 0.58	6.82 ± 0.61	13.88 ± 1.53	4.16 ± 1.16	7.84 ± 1.16	11.88 ± 1.16
7c	5.34 ± 0.58	10.00 ± 2.00	17.28 ± 1.53	5.14 ± 0.58	8.48 ± 0.58	14.84 ± 0.58
8a	7.14 ± 0.47	13.72 ± 0.58	19.28 ± 0.47	6.64 ± 0.58	11.84 ± 1.73	18.42 ± 1.16
8b	6.82 ± 0.58	12.88 ± 0.61	19.36 ± 0.61	7.23 ± 0.58	13.00 ± 0.00	18.38 ± 0.27
8c	7.26 ± 0.58	14.00 ± 2.00	21.86 ± 1.53	7.38 ± 0.27	14.26 ± 0.58	20.66 ± 0.58
9a	7.68 ± 0.58	14.46 ± 1.16	21.68 ± 1.16	6.68 ± 0.58	12.57 ± 0.58	20.48 ± 1.73
9b	8.14 ± 0.47	14.75 ± 0.58	21.72 ± 1.53	7.14 ± 0.58	12.44 ± 0.58	20.96 ± 0.58
9c	8.82 ± 0.58	16.58 ± 0.58	23.76 ± 1.53	7.36 ± 0.58	13.00 ± 0.00	22.66 ± 0.58
10a	5.44 ± 0.58	9.20 ± 0.58	11.16 ± 1.16	5.38 ± 1.73	10.12 ± 0.61	12.16 ± 0.61
10b	4.12 ± 0.58	8.30 ± 0.47	10.00 ± 2.00	4.24 ± 0.47	8.10 ± 0.58	10.36 ± 1.53
10c	5.62 ± 0.58	10.83 ± 0.61	13.46 ± 1.53	5.06 ± 0.58	9.80 ± 0.61	13.10 ± 0.58
11a	4.35 ± 0.58	8.72 ± 1.16	11.72 ± 1.16	4.56 ± 2.08	8.24 ± 1.16	12.26 ± 2.08
11b	4.62 ± 0.58	8.02 ± 2.08	12.10 ± 1.16	4.90 ± 0.58	7.58 ± 1.16	10.78 ± 1.53
11c	5.04 ± 0.58	9.86 ± 1.16	13.14 ± 1.53	5.14 ± 0.58	9.06 ± 0.63	12.40 ± 0.58
12a	5.86 ± 0.58	9.48 ± 1.63	12.46 ± 1.53	5.10 ± 0.58	10.12 ± 0.27	12.94 ± 0.47
12b	4.10 ± 0.58	7.46 ± 0.47	10.20 ± 1.53	5.24 ± 0.58	9.62 ± 0.27	11.12 ± 0.58
12c	5.38 ± 0.58	9.30 ± 0.27	12.70 ± 0.63	5.60 ± 0.58	8.74 ± 0.61	13.16 ± 1.16
13a	5.19 ± 0.61	10.26 ± 1.73	14.81 ± 1.53	5.16 ± 0.47	7.13 ± 0.58	13.14 ± 0.61
13b	5.48 ± 0.58	10.41 ± 1.16	14.65 ± 0.61	4.80 ± 0.58	6.96 ± 0.47	12.28 ± 0.58
13c	5.41 ± 0.58	10.96 ± 0.61	14.82 ± 0.58	5.21 ± 0.58	8.12 ± 1.16	14.19 ± 0.58
14a	5.58 ± 1.73	11.26 ± 0.61	15.21 ± 1.16	5.32 ± 0.53	9.72 ± 0.61	14.46 ± 1.53
14b	5.43 ± 0.58	10.92 ± 1.16	14.79 ± 1.53	5.21 ± 0.47	9.64 ± 0.61	14.32 ± 0.58
14c	5.89 ± 0.47	11.14 ± 0.27	15.75 ± 1.16	5.48 ± 0.58	10.42 ± 0.47	15.32 ± 0.58
15a	4.61 ± 0.47	8.82 ± 0.29	13.44 ± 1.16	4.89 ± 0.61	9.17 ± 0.47	12.31 ± 0.27
15b	4.70 ± 1.16	8.12 ± 0.53	13.12 ± 0.47	4.68 ± 0.61	9.12 ± 0.27	12.15 ± 0.53
15c	5.24 ± 0.47	9.16 ± 1.73	14.81 ± 0.27	5.10 ± 0.58	9.42 ± 0.61	13.15 ± 0.47
16a	4.30 ± 1.16	7.40 ± 1.73	12.61 ± 0.27	4.71 ± 0.61	7.65 ± 0.58	12.88 ± 0.47
16b	4.18 ± 0.61	7.10 ± 1.16	12.05 ± 0.58	4.35 ± 0.47	7.90 ± 0.61	12.62 ± 0.58
16c	4.50 ± 0.58	8.06 ± 0.61	13.25 ± 0.47	4.93 ± 0.53	8.08 ± 0.61	13.71 ± 0.53
Griseofulvin	–	–	24.67 ± 1.16	–	–	23.14 ± 0.17

[a] Zone of inhibition in millimeter.
[b] SD = standard deviation.

refluxing mixture as a solvent in order to homogenise solution. The resulting mixture was further allowed to reflux for 6 h. Excess ethanol was distilled out and the contents were allowed to cool. The crystals formed were filtered, washed thoroughly with water and dried. The completion of the reaction was monitored on TLC by using silica gel-G coated plates by using ethyl acetate and petroleum ether (1:1) as the eluent and observed under UV light.

*5.2. General procedure for the preparation of 2-aryl substituted-5-mercapto-1,3,4-oxadiazole (**2**)*

To a solution of **1** (0.1 M) in ethanol (30 ml), KOH (0.1 M) in absolute ethanol (50 ml) and CS_2 (0.2 M) were added and refluxed for about 5 h till evolution of hydrogen sulfide was ceased. The reaction mixture was cooled at room temperature and diluted with water. On acidification with dilute hydrochloric acid, the required oxadiazole was precipitated. It was filtered, thoroughly washed with cold water and recrystallised from ethanol.

*5.3. General procedure for the preparation of 3-substituted-4-amino-5-mercapto-1,2,4-triazole **3a–c***

A mixture of **2** (0.1 M) and hydrazine hydrate (0.1 M) in dry pyridine (15 ml) was refluxed for about 4 h. The reaction mixture was cooled at room temperature and was neutralized with dilute hydrochloric acid. The solid obtained was filtered,

Table 8
Antibacterial activity of compounds[a] (**3**–**16**)

Compound	*Escherichia coli*			*Pseudomonas aeruginosa*			*Bacillus subtilis*			*Staphylococcus aureus*		
	10 (μg/ml) ± SD[b]	20 (μg/ml) ± SD[b]	30 (μg/ml) ± SD[b]	10 (μg/ml) ± SD[b]	20 (μg/ml) ± SD[b]	30 (μg/ml) ± SD[b]	10 (μg/ml) ± SD[b]	20 (μg/ml) ± SD[b]	30 (μg/ml) ± SD[b]	10 (μg/ml) ± SD[b]	20 (μg/ml) ± SD[b]	30 (μg/ml) ± SD[b]
3a	5.08 ± 0.26	7.16 ± 0.58	9.17 ± 0.45	5.23 ± 0.26	7.26 ± 1.16	9.10 ± 2.09	4.25 ± 0.61	7.05 ± 0.58	10.11 ± 1.53	5.16 ± 0.58	7.28 ± 0.17	9.06 ± 0.58
3b	4.86 ± 1.16	7.58 ± 0.58	10.06 ± 0.58	5.06 ± 1.16	6.76 ± 0.26	8.24 ± 0.58	5.06 ± 0.45	7.26 ± 0.61	9.83 ± 1.16	4.72 ± 0.47	7.14 ± 0.58	9.52 ± 0.61
3c	6.74 ± 1.16	9.16 ± 1.53	12.85 ± 2.09	6.12 ± 0.58	9.16 ± 0.47	12.78 ± 0.61	5.80 ± 0.26	8.94 ± 1.53	11.21 ± 1.53	5.46 ± 1.16	8.16 ± 2.09	11.26 ± 1.53
4a	6.86 ± 1.73	11.72 ± 2.52	16.52 ± 2.65	6.72 ± 1.16	11.38 ± 0.61	15.49 ± 0.58	6.82 ± 0.47	11.15 ± 1.16	16.16 ± 1.53	5.82 ± 0.45	10.12 ± 0.61	16.36 ± 0.37
4b	6.08 ± 1.73	11.28 ± 2.52	16.86 ± 2.89	5.92 ± 1.16	10.85 ± 1.53	16.04 ± 0.58	5.76 ± 1.71	10.24 ± 0.61	15.92 ± 0.45	5.12 ± 0.58	10.26 ± 0.17	16.74 ± 1.16
4c	7.64 ± 1.16	13.18 ± 0.58	17.36 ± 1.53	7.12 ± 0.26	12.04 ± 0.58	17.26 ± 1.16	6.16 ± 2.09	11.84 ± 0.58	16.86 ± 2.89	6.18 ± 0.26	12.69 ± 0.58	17.48 ± 2.09
5a	5.16 ± 0.58	9.12 ± 0.58	16.67 ± 1.53	5.31 ± 0.45	10.26 ± 0.58	16.11 ± 1.16	7.06 ± 1.16	11.10 ± 0.58	16.38 ± 1.73	6.89 ± 0.58	12.06 ± 0.61	16.10 ± 0.26
5b	5.25 ± 1.16	8.80 ± 0.47	16.00 ± 0.00	5.26 ± 0.58	10.12 ± 1.16	16.05 ± 2.09	6.29 ± 1.16	10.18 ± 1.73	16.12 ± 0.45	6.72 ± 0.17	11.68 ± 1.16	16.60 ± 0.26
5c	6.28 ± 0.58	10.48 ± 1.16	17.00 ± 2.00	6.00 ± 1.00	11.84 ± 1.53	16.82 ± 0.45	7.38 ± 2.09	12.48 ± 0.45	17.10 ± 1.53	7.10 ± 0.61	13.73 ± 0.58	17.92 ± 0.61
6a	8.28 ± 0.58	14.48 ± 1.16	18.78 ± 0.58	7.82 ± 2.09	13.27 ± 0.17	18.71 ± 0.58	7.68 ± 1.53	13.06 ± 0.45	18.80 ± 1.71	7.21 ± 0.58	13.19 ± 1.16	18.12 ± 0.58
6b	7.85 ± 0.26	14.36 ± 0.58	18.64 ± 1.16	7.70 ± 1.16	14.10 ± 0.58	18.16 ± 1.73	7.40 ± 1.53	13.26 ± 1.16	18.66 ± 1.53	6.96 ± 0.58	12.61 ± 1.16	18.27 ± 0.26
6c	8.74 ± 0.17	15.27 ± 0.58	19.41 ± 1.16	8.17 ± 1.16	14.15 ± 2.09	19.10 ± 0.58	8.14 ± 1.16	14.10 ± 0.58	19.79 ± 1.16	8.16 ± 0.26	14.10 ± 0.58	19.12 ± 1.16
7a	4.18 ± 2.09	8.00 ± 2.00	13.15 ± 0.58	4.84 ± 0.26	9.06 ± 1.16	13.28 ± 0.58	4.70 ± 1.53	8.38 ± 0.58	13.78 ± 1.16	4.57 ± 0.58	8.82 ± 1.16	13.70 ± 0.26
7b	4.26 ± 0.45	8.10 ± 0.58	13.27 ± 1.16	4.63 ± 1.16	8.90 ± 0.17	13.10 ± 1.73	4.58 ± 1.16	8.12 ± 0.17	13.89 ± 1.53	4.61 ± 0.58	8.93 ± 0.63	13.87 ± 0.26
7c	5.38 ± 0.47	8.79 ± 0.58	14.10 ± 1.16	5.95 ± 1.16	9.81 ± 1.53	14.23 ± 0.58	6.02 ± 1.16	10.41 ± 0.58	14.85 ± 2.62	6.07 ± 0.58	10.80 ± 1.76	14.51 ± 0.45
8a	6.39 ± 0.61	12.23 ± 1.16	19.21 ± 2.09	7.02 ± 0.45	12.48 ± 0.58	19.11 ± 0.61	7.12 ± 1.53	13.84 ± 0.17	18.63 ± 0.63	6.98 ± 0.26	13.70 ± 1.16	18.58 ± 1.53
8b	6.72 ± 0.26	12.82 ± 0.58	19.67 ± 1.16	6.93 ± 2.09	12.19 ± 0.58	19.39 ± 1.73	7.19 ± 1.16	13.92 ± 1.53	18.91 ± 1.53	7.05 ± 0.37	13.61 ± 0.26	18.14 ± 1.16
8c	7.48 ± 0.47	14.78 ± 0.58	20.19 ± 1.16	7.79 ± 0.26	13.78 ± 0.45	20.59 ± 0.61	7.82 ± 1.16	14.55 ± 0.17	20.38 ± 0.47	7.82 ± 2.09	14.66 ± 0.45	19.23 ± 1.53
9a	8.10 ± 2.09	14.65 ± 1.16	19.67 ± 0.47	8.68 ± 1.16	14.92 ± 2.09	19.52 ± 0.26	7.78 ± 1.53	14.12 ± 0.58	19.16 ± 0.63	7.29 ± 0.45	14.11 ± 1.16	19.25 ± 0.61
9b	7.96 ± 0.17	14.39 ± 0.45	19.29 ± 1.16	8.21 ± 1.53	14.88 ± 0.58	19.26 ± 1.73	7.64 ± 1.16	14.38 ± 2.09	19.26 ± 1.53	7.10 ± 0.17	13.85 ± 1.71	19.19 ± 0.58
9c	8.54 ± 1.71	14.27 ± 0.58	20.79 ± 1.16	8.39 ± 1.16	15.21 ± 0.26	21.29 ± 0.58	8.12 ± 1.16	14.76 ± 0.58	19.86 ± 1.16	7.90 ± 0.58	14.18 ± 0.58	20.17 ± 0.47
10a	5.10 ± 0.58	8.39 ± 0.47	13.15 ± 0.17	4.83 ± 0.61	9.18 ± 2.09	12.80 ± 0.26	4.76 ± 1.53	8.79 ± 0.58	13.17 ± 1.16	4.58 ± 0.63	8.52 ± 1.16	13.72 ± 0.58
10b	4.72 ± 0.45	8.49 ± 1.71	12.90 ± 1.16	4.90 ± 1.16	8.42 ± 0.58	12.27 ± 1.73	4.92 ± 1.16	8.18 ± 1.16	13.65 ± 1.53	4.82 ± 2.09	8.39 ± 0.61	13.60 ± 0.17
10c	5.16 ± 0.61	9.35 ± 0.58	14.16 ± 1.16	5.36 ± 1.16	9.62 ± 0.58	14.49 ± 0.58	5.82 ± 1.16	9.61 ± 0.58	14.15 ± 0.61	4.85 ± 0.58	9.10 ± 0.58	13.27 ± 0.47
11a	4.26 ± 0.26	7.28 ± 0.47	12.28 ± 0.61	4.15 ± 0.17	7.92 ± 2.09	12.37 ± 0.58	4.12 ± 1.53	7.18 ± 0.47	11.91 ± 0.47	4.17 ± 0.61	8.12 ± 1.16	12.12 ± 0.17
11b	4.48 ± 0.58	7.42 ± 0.58	12.36 ± 1.16	4.04 ± 1.16	7.42 ± 0.58	12.62 ± 1.73	4.07 ± 2.09	7.21 ± 1.16	12.28 ± 1.53	4.06 ± 0.71	8.08 ± 0.45	12.02 ± 0.17
11c	5.12 ± 0.47	9.10 ± 0.58	13.84 ± 1.16	4.92 ± 1.53	8.14 ± 0.45	14.62 ± 0.61	4.60 ± 1.16	8.38 ± 0.58	13.25 ± 2.00	4.89 ± 0.58	9.12 ± 2.09	13.29 ± 1.53
12a	4.78 ± 0.26	8.12 ± 1.16	12.39 ± 0.58	4.12 ± 0.58	8.16 ± 0.61	12.19 ± 2.09	4.33 ± 1.53	7.60 ± 0.45	12.29 ± 1.16	4.80 ± 0.47	7.59 ± 1.16	12.58 ± 0.58
12b	4.90 ± 0.17	8.22 ± 2.09	12.52 ± 1.16	4.25 ± 1.73	8.23 ± 0.58	12.37 ± 1.73	4.33 ± 1.16	7.32 ± 1.16	12.67 ± 1.53	4.59 ± 0.45	7.38 ± 0.61	12.18 ± 0.26
12c	5.78 ± 0.61	9.18 ± 0.58	13.62 ± 1.16	4.85 ± 1.73	8.90 ± 0.58	13.48 ± 0.45	5.67 ± 1.16	8.75 ± 2.09	13.79 ± 0.61	5.12 ± 0.58	8.19 ± 0.17	13.49 ± 0.47
13a	4.12 ± 0.58	7.39 ± 0.45	14.37 ± 0.61	4.82 ± 0.58	8.95 ± 0.45	14.15 ± 1.16	4.39 ± 0.178	7.68 ± 0.47	13.57 ± 1.53	4.82 ± 0.61	8.61 ± 0.47	14.12 ± 0.17
13b	4.29 ± 0.47	7.49 ± 1.16	14.25 ± 0.26	3.73 ± 1.53	7.11 ± 0.26	12.68 ± 0.17	3.80 ± 1.16	6.65 ± 1.16	12.16 ± 1.73	3.70 ± 0.58	7.31 ± 0.63	11.81 ± 0.58
13c	4.82 ± 0.58	8.04 ± 0.63	15.16 ± 1.16	6.67 ± 1.53	12.33 ± 0.58	17.67 ± 1.16	5.33 ± 0.47	10.67 ± 1.53	11.33 ± 2.09	6.67 ± 1.73	12.33 ± 0.61	13.33 ± 0.58
14a	5.21 ± 0.58	10.11 ± 0.58	15.12 ± 1.53	4.88 ± 0.58	7.36 ± 0.58	13.21 ± 1.73	5.12 ± 0.58	8.71 ± 1.73	13.61 ± 1.53	5.20 ± 1.73	8.82 ± 0.58	14.21 ± 0.58
14b	5.16 ± 1.71	10.03 ± 1.16	14.96 ± 1.16	4.42 ± 1.53	7.88 ± 0.58	13.13 ± 0.45	4.92 ± 1.16	8.49 ± 1.53	13.50 ± 1.73	5.10 ± 0.47	8.37 ± 0.61	14.02 ± 0.58
14c	5.78 ± 0.58	11.02 ± 0.47	16.85 ± 1.16	6.12 ± 1.73	11.82 ± 0.58	17.14 ± 1.16	6.25 ± 2.09	11.52 ± 1.73	17.23 ± 0.47	6.11 ± 0.75	11.51 ± 0.61	17.48 ± 1.16
15a	4.71 ± 0.47	7.90 ± 0.58	14.27 ± 1.73	1.33 ± 0.58	4.33 ± 0.58	8.00 ± 0.00	1.67 ± 0.58	4.00 ± 0.00	8.33 ± 1.53	1.33 ± 0.61	4.33 ± 0.47	8.33 ± 0.45
15b	4.48 ± 1.53	7.18 ± 2.09	14.18 ± 1.16	7.33 ± 1.53	11.66 ± 0.58	13.30 ± 0.58	4.32 ± 1.16	8.32 ± 1.16	12.00 ± 1.73	4.02 ± 0.61	7.64 ± 0.47	10.60 ± 0.58
15c	5.11 ± 0.58	8.42 ± 0.26	15.65 ± 1.16	6.67 ± 0.63	12.33 ± 0.26	14.67 ± 1.16	5.33 ± 0.58	10.67 ± 0.37	16.33 ± 0.45	4.60 ± 2.09	8.12 ± 0.61	12.26 ± 0.17
16a	3.82 ± 0.26	6.90 ± 0.58	10.12 ± 0.47	3.90 ± 0.45	7.10 ± 0.17	11.90 ± 1.73	3.60 ± 0.58	6.82 ± 0.47	9.33 ± 1.53	3.82 ± 0.47	6.10 ± 2.09	11.04 ± 0.26
16b	3.95 ± 1.79	6.71 ± 1.16	10.17 ± 1.16	4.12 ± 1.53	7.48 ± 0.26	11.39 ± 0.58	3.30 ± 1.16	6.30 ± 2.09	9.12 ± 1.73	3.74 ± 0.61	5.92 ± 0.61	10.61 ± 0.47
16c	4.11 ± 0.58	7.19 ± 0.47	12.10 ± 1.16	4.36 ± 0.61	7.90 ± 0.58	13.18 ± 1.16	4.52 ± 0.58	7.48 ± 1.53	11.38 ± 0.47	4.42 ± 0.26	6.23 ± 0.61	11.19 ± 0.58
Chloramphenicol	–	–	–	–	–	–	–	–	24.61 ± 0.27	–	–	26.12 ± 0.17
Chloramphenicol	–	–	23.67 ± 0.47	–	–	25.39 ± 1.73	–	–	–	–	–	–

[a] Zone of inhibition in millimeter.
[b] SD = standard deviation.

Table 9
Anti-inflammatory activity of compounds (**4–16**)

Compound	Change in paw volume (in ml) after (±SE)[a]				Percentage inhibition of oedema volume after			
	1 h	2 h	3 h	4 h	1 h	2 h	3 h	4 h
4a	0.64 ± 0.02	0.95 ± 0.03	1.06 ± 0.04	1.65 ± 0.01	11.64	17.24	20.12	24.46
4b	0.61 ± 0.03	0.97 ± 0.03	1.33 ± 0.01	1.60 ± 0.02	12.35	18.68	20.17	22.21
4c	0.70 ± 0.02	1.00 ± 0.00	1.41 ± 0.03	1.66 ± 0.02	11.76	14.46	16.45	24.45
5a	0.61 ± 0.03	0.83 ± 0.03	1.10 ± 0.02	1.48 ± 0.04	08.68	20.18	24.07	27.45
5b	0.53 ± 0.03	0.77 ± 0.01	1.15 ± 0.03	1.48 ± 0.02	10.16	13.25	21.22	24.86
5c	0.54 ± 0.02	0.80 ± 0.02	1.14 ± 0.02	1.42 ± 0.02	07.23	13.44	18.61	26.34
6a	0.80 ± 0.02	1.10 ± 0.04	1.47 ± 0.03	1.78 ± 0.04	11.11	14.26	18.55	20.88
6b	0.68 ± 0.02	0.97 ± 0.03	1.42 ± 0.02	1.55 ± 0.05	14.62	17.15	19.08	24.79
6c	0.70 ± 0.02	0.97 ± 0.03	1.40 ± 0.04	1.58 ± 0.04	12.50	17.09	20.28	23.37
7a	0.73 ± 0.03	1.00 ± 0.00	1.38 ± 0.04	1.58 ± 0.02	08.35	14.23	20.97	23.37
7b	0.72 ± 0.02	1.02 ± 0.04	1.45 ± 0.03	1.53 ± 0.05	10.54	12.86	17.14	20.79
7c	0.75 ± 0.03	1.03 ± 0.03	1.53 ± 0.03	1.78 ± 0.02	06.25	11.40	16.47	21.69
8a	0.46 ± 0.02	0.72 ± 0.04	1.05 ± 0.03	1.56 ± 0.04	14.42	20.15	23.48	27.24
8b	0.56 ± 0.02	1.00 ± 0.00	1.28 ± 0.04	1.64 ± 0.02	11.16	13.25	22.50	24.18
8c	0.53 ± 0.03	0.77 ± 0.03	1.05 ± 0.03	1.43 ± 0.03	10.06	15.34	24.12	27.10
9a	0.73 ± 0.03	0.97 ± 0.03	1.33 ± 0.03	1.62 ± 0.02	18.52	24.65	25.94	28.13
9b	0.80 ± 0.02	1.10 ± 0.04	1.50 ± 0.04	1.77 ± 0.03	11.11	14.26	16.66	21.46
9c	0.75 ± 0.05	1.05 ± 0.03	1.43 ± 0.03	1.70 ± 0.04	16.66	18.16	20.38	24.44
10a	0.74 ± 0.02	1.05 ± 0.07	1.36 ± 0.02	1.46 ± 0.02	6.10	14.38	21.35	33.87**
10b	0.73 ± 0.03	1.12 ± 0.02	1.24 ± 0.02	1.42 ± 0.04	04.11	11.60	19.14	29.62*
10c	0.62 ± 0.02	0.84 ± 0.02	1.04 ± 0.06	1.26 ± 0.02	15.96	20.10	26.14	30.82*
11a	0.60 ± 0.04	0.90 ± 0.02	1.10 ± 0.02	1.18 ± 0.02	11.32	20.03	26.05	32.66**
11b	0.70 ± 0.02	0.98 ± 0.04	1.16 ± 0.02	1.38 ± 0.02	10.46	16.16	21.42	28.42*
11c	0.68 ± 0.02	0.94 ± 0.02	1.08 ± 0.02	1.16 ± 0.04	19.69	24.82	29.40	31.16**
12a	0.70 ± 0.04	0.98 ± 0.02	1.14 ± 0.04	1.26 ± 0.04	08.80	16.48	21.35	34.68**
12b	0.68 ± 0.02	0.90 ± 0.05	1.10 ± 0.02	1.32 ± 0.04	16.10	26.78	28.32	28.48*
12c	0.62 ± 0.02	0.78 ± 0.06	1.14 ± 0.02	1.36 ± 0.02	15.96	21.54	26.52	30.02*
13a	0.77 ± 0.03	0.91 ± 0.03	1.25 ± 0.05	1.67 ± 0.03	13.9	18.7	23.1	25.64
13b	0.79 ± 0.03	0.92 ± 0.02	1.26 ± 0.04	1.70 ± 0.04	12.0	17.5	21.1	24.60
13c	0.71 ± 0.03	0.88 ± 0.02	1.23 ± 0.07	1.67 ± 0.05	16.4**	21.6*	24.1	25.93
14a	0.76 ± 0.02	0.91 ± 0.03	1.27 ± 0.03	1.71 ± 0.03	15.6**	18.5	21.7	24.20
14b	0.77 ± 0.03	0.92 ± 0.02	1.27 ± 0.05	1.72 ± 0.02	14.5*	17.6	21.4	23.71
14c	0.76 ± 0.04	0.92 ± 0.02	1.25 ± 0.03	1.69 ± 0.03	15.6**	18.1	22.8	24.94
15a	0.78 ± 0.04	0.95 ± 0.03	1.32 ± 0.04	1.79 ± 0.05	12.8*	15.2	18.4	20.62
15b	0.78 ± 0.02	0.94 ± 0.02	1.33 ± 0.03	1.79 ± 0.07	13.2*	15.9	17.7	21.47
15c	0.78 ± 0.02	0.92 ± 0.02	1.29 ± 0.03	1.74 ± 0.04	13.7*	18.2	20.3	22.70
16a	0.77 ± 0.05	0.93 ± 0.07	1.32 ± 0.02	1.79 ± 0.03	14.1*	16.8	18.5	20.68
16b	0.78 ± 0.02	0.94 ± 0.02	1.30 ± 0.05	1.80 ± 0.04	13.4*	15.8	18.4	19.92
16c	0.77 ± 0.03	0.91 ± 0.03	1.27 ± 0.05	1.75 ± 0.03	14.6*	18.9	21.5	22.35
Phenylbutazone	0.72 ± 0.02	0.92 ± 0.02	0.97 ± 0.03	1.00 ± 0.00	21.24***	33.59***	40.81***	45.40***

For all other comparisons $P > 0.05$.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
[a] ± Standard error.

thoroughly washed with cold water and recrystallised from ethanol.

5.4. Conventional procedure for the synthesis of 3-aryl/aralkyl/heteroaryl-6-(2-substituted-4-quinolinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (*4a*)

An equimolar mixture of respective triazole (0.02 M) and 2-phenyl-quinoline-4-carboxylic acid (0.02 M) was dissolved in 10 ml of dry phosphorous oxychloride. The resulted solution was further heated under reflux for 7 h. The reaction mixture was cooled to room temperature and the mixture was gradually poured onto crushed ice with stirring. Finely powdered potassium carbonate and the required amount of solid potassium hydroxide were added till the pH of the mixture was raised to 8, to remove the excess of phosphorous oxychloride. The mixture was allowed to stand overnight and the solid was separated. It was filtered, washed thoroughly with cold water, dried and recrystallised from a mixture of DMF and ethanol. Similarly other compounds were synthesized and characterized by various spectral studies.

5.5. Microwave method for the synthesis of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (Scheme 3)

A solution of **3a–c** (0.01 M) and respective aromatic acids in phosphorous oxychloride was prepared. Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina

Table 10
Analgesic activity of compounds (**4–16**)

Compound	Reaction time (s) after drug administration			Percent increase in reaction time		
	30 min ± SE[a]	60 min ± SE[a]	90 min ± SE[a]	30 min	60 min	90 min
4a	6.17 ± 0.47	6.85 ± 0.56	8.70 ± 0.37	5.34	15.68	26.85
4b	5.20 ± 0.21	5.84 ± 0.42	6.71 ± 0.50	5.36	17.26	25.11
4c	5.43 ± 0.26	6.37 ± 0.55	7.03 ± 0.27	4.86	14.48	21.10
5a	6.43 ± 0.15	7.67 ± 0.42	8.00 ± 0.45	7.60	12.65	21.06
5b	6.24 ± 0.48	7.14 ± 0.51	8.16 ± 0.42	5.96	11.05	20.14
5c	6.33 ± 0.33	7.40 ± 0.48	8.22 ± 0.17	6.04	11.35	20.34
6a	4.46 ± 0.34	4.92 ± 0.55	5.26 ± 0.48	7.69	17.24	23.84
6b	4.50 ± 0.34	5.00 ± 0.37	5.33 ± 0.21	7.55	16.80	21.96
6c	4.50 ± 0.60	5.20 ± 0.42	8.37 ± 0.34	5.62	10.24	19.24
7a	6.24 ± 0.34	6.92 ± 0.42	7.84 ± 0.34	5.68	15.18	26.14
7b	5.83 ± 0.31	6.67 ± 0.38	7.33 ± 0.34	5.71	14.10	23.45
7c	5.00 ± 0.40	5.17 ± 0.34	5.83 ± 0.32	4.35	11.45	19.35
8a	5.54 ± 0.17	7.67 ± 0.21	8.00 ± 0.40	7.14	17.45	23.00
8b	6.17 ± 0.52	7.67 ± 0.45	7.67 ± 0.60	6.24	12.55	23.89
8c	7.65 ± 0.33	8.46 ± 0.31	8.46 ± 0.21	6.04	11.35	20.34
9a	8.17 ± 0.31	8.83 ± 0.48	9.83 ± 0.17	4.12	11.35	20.34
9b	6.00 ± 0.73	6.50 ± 0.43	7.50 ± 0.35	2.83	10.30	22.66
9c	5.87 ± 0.33	8.24 ± 0.60	9.17 ± 0.31	4.13	6.20	16.43
10a	6.50 ± 0.43	7.67 ± 0.33	9.67 ± 0.22	13.69	23.76	31.48*
10b	4.33 ± 0.42	5.00 ± 0.26	5.83 ± 0.31	11.92	19.06	28.32*
10c	7.50 ± 0.43	9.00 ± 0.58	10.67 ± 0.42	13.84	24.76	31.86*
11a	4.56 ± 0.26	6.17 ± 0.48	7.67 ± 0.21	19.48	28.54*	35.24**
11b	4.33 ± 0.42	5.00 ± 0.10	5.83 ± 0.31	19.23	27.82*	29.04*
11c	7.33 ± 0.56	8.67 ± 0.50	10.17 ± 0.61	9.18	23.17	33.49**
12a	5.17 ± 0.70	6.17 ± 0.48	7.67 ± 0.21	19.48	28.32*	34.24**
12b	6.33 ± 0.50	7.33 ± 0.42	9.00 ± 0.12	13.16	25.00*	31.88*
12c	6.33 ± 0.43	9.00 ± 0.00	10.67 ± 0.42	6.66	22.22	35.33**
13a	6.17 ± 0.55	7.67 ± 0.45	7.67 ± 0.61	6.24	12.55	23.89
13b	5.43 ± 0.21	6.37 ± 0.55	7.03 ± 0.18	5.36	17.26	25.11
13c	6.24 ± 0.34	6.92 ± 0.42	7.84 ± 0.34	5.68	15.18	26.14
14a	5.83 ± 0.17	6.67 ± 0.70	7.33 ± 0.64	5.71	14.10	23.45
14b	6.00 ± 0.73	6.50 ± 0.43	7.50 ± 0.35	2.83	10.30	22.66
14c	6.17 ± 0.34	6.85 ± 0.56	8.70 ± 0.37	5.34	15.68	26.85
15a	5.20 ± 0.33	5.84 ± 0.55	6.71 ± 0.45	4.86	14.48	21.10
15b	6.43 ± 0.33	7.67 ± 0.67	8.00 ± 0.06	7.60	12.65	21.06
15c	5.54 ± 0.31	7.67 ± 0.34	8.00 ± 0.45	7.14	17.45	23.00
16a	5.54 ± 0.33	8.17 ± 0.60	9.17 ± 0.31	4.38	6.20	19.67
16b	4.50 ± 0.24	5.20 ± 0.45	8.37 ± 0.34	5.62	10.24	19.24
16c	4.50 ± 0.34	5.00 ± 0.37	5.33 ± 0.21	7.55	16.80	21.96
Diclofenac sodium	5.67 ± 0.50	6.50 ± 0.43	7.33 ± 0.21	32.23***	38.15***	43.25***

For all other comparisons $P > 0.05$.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
[a] Standard error.

bath and subjected to microwave irradiation intermittently at 30 s for 7–8 min. The mixture was cooled and then poured onto crushed ice cubes. Finely powdered potassium carbonate and the required amount of solid potassium hydroxide were added till the pH of the mixture was raised to 8, to remove the excess of phosphorous oxychloride. The solid thus separated was filtered, washed thoroughly with cold water, dried and recrystallised from a mixture of DMF and ethanol (2:1).

*5.6. Conventional procedure for the preparation of 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **13–16** (**a–c**) (Scheme 4)*

An equimolecular mixture of substituted triazole (0.02 M) and 2-furfuraldehyde (0.02 M) (**13a**), dry DMF (30 ml) and a catalytic amount of *p*-toluenesulphonic acid (10 mg) was taken in a round bottom flask. The mixture was refluxed for about 10–12 h, concentrated to half its volume and cooled to room temperature. The cooled mixture was poured gradually onto crushed ice cubes with stirring. The mixture was allowed to stand and solid was separated. It was filtered, washed thoroughly with cold water, dried and recrystallised from hot ethanol.

5.7. Microwave method for the synthesis of 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (Scheme 5)

A solution of **3a–c** (0.01 M), respective hetero aromatic aldehyde (0.01 M) and *p*-toluenesulphonic acid (10 mg) in dry DMF (30 ml) was prepared. The resulting solution was adsorbed over 20 g of acidic alumina at room temperature.

The reaction mixture was mixed, dried and kept inside the alumina bath and subjected to microwave irradiation at an interval of 30 s for 6–7 min. The mixture was cooled and then the product was extracted with dry toluene and cooled. The solid thus separated was filtered, washed thoroughly with water and recrystallised from ethanol.

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