Studies on Synthesis of Novel Triazole Tagged Pyrazole Fused Naphthalene 5-Thiazine-5,5-dioxide Derivatives, Their Antimicrobial, and Antioxidant Activity

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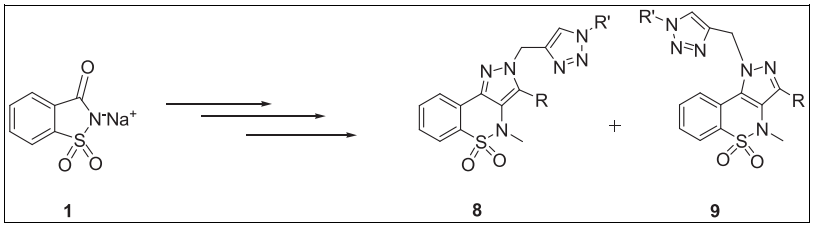

A series of novel triazole tagged pyrazole fused naphthalene-5-thiazine-5,5-dioxide derivatives **8** and **9** were synthesized starting from sodium salt of saccharin **1**. The structure of each intermediate and products was established on the basis of spectroscopy data. All the synthesized compounds **8** and **9** were screened against various bacterial and fungal strains but found to show no activity up to 150-μg/mL concentration. Further screening for antioxidant property resulted promising compounds.

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INTRODUCTION

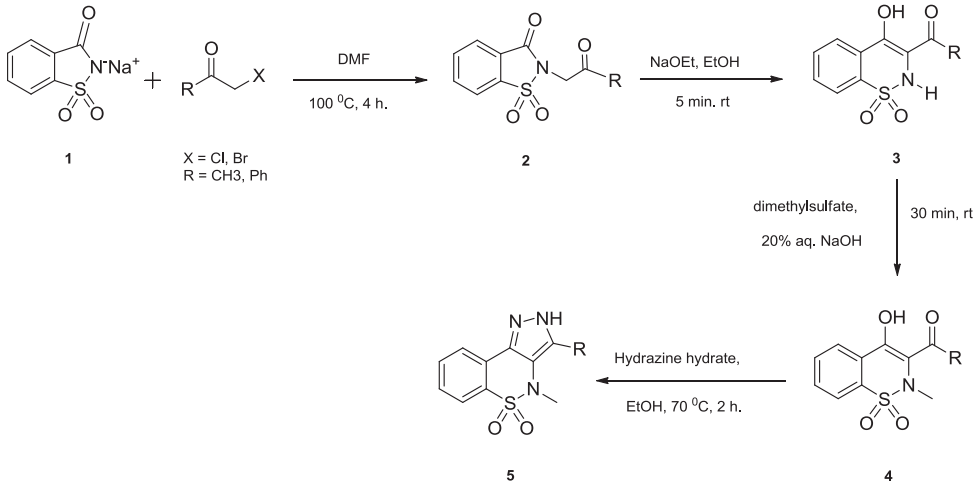
Pyrazole nucleus present in many biologically active compounds are known to have antibacterial, antifungal [1], antiviral [2], anti-arrhythmic [3], anti-inflammatory [4], hypoglycemic [5], and herbicidal [6] activities. 1,2-Benzothiazine-1,1-dioxides are also considered as another class of potential molecules exemplified as piroxicam [7], ampiroxicam [8], and meloxicam [9] and used all over the world as nonsteroidal anti-inflammatory drugs. Some of the 1,2-benzothiazine-3-ylquinazolin-4(3*H*)-ones possess 11β-HSD1 inhibitors [10] and antibacterial [11,12] and antioxidant activities [13]. Similarly, the perfluoroalkyl triazoles [14,15] and fluoroalkyl derivatives [16–18] also show promising biological activity. Recently, pyrazole fused [19] and benzylidene substituted [13] 1,2-benzothiazine-1,1-dioxides were reported as promising antibacterial/antioxidative agents. Keeping in view the importance of all the above basic skeletons and in continuation of our recent efforts on click chemistry [20–22], we designed the synergism of three nuclei such as pyrazole, 1,2-benzothiazine-1,1-dioxide, and triazole in a single molecule to have a promising activity. Thus, in the present paper, we have synthesized a novel series of perfluoroalkyl triazole tagged pyrazole fused naphthalene-5-thiazine-5,5-dioxide derivatives, screened them for antimicrobial and antioxidant activities, and reported them here for the first time.

CHEMISTRY

The synthetic sequence involves reaction of sodium salt of saccharin **1** with α–halo Ketones in DMF at 110°C to give *N*-alkylated product **2** followed by reaction with sodium ethoxide in ethanol, which resulted in ring expansion and formed 1,2-benzothiazine-1,1-dioxide derivatives **3**. The compound **3** was *N*-alkylated with dimethyl sulfate to give products **4** and was reacted with hydrazine hydrate to form pyrazole fused benzene sulfonamide derivatives **5** [19]. The structure of product **5** is in two canonical forms, and on reaction with propargyl bromide, product **5** resulted *N*-propargylated regioisomers **6** and **7** in definite proportions. When $R = CH_3$, the ratio of **6**:**7** is 80:20, whereas when $R = C_6H_5$, the ratio is 60:40. The polarity of both the regioisomers **6** and **7** makes them very close, and they could not be separated; however, the mixtures **6** and **7** were further cyclized with alkyl/aryl azides by Click reaction under Sharpless conditions [23,24] and obtained exclusively triazole alkyl tagged pyrazole fused naphthalene-5-thiazine- 5,5-dioxide derivatives **8** and **9**, respectively. Compounds **8** and **9** were separated and identified by spectral data. The reaction steps are outlined in Schemes 1 and 2, and products are tabulated in Tables 1 and 2.

The structure of two sets of compounds **8** and **9** when R = Me and R = ph were identified by ^{1}H NMR (600 MHz) in $CDCl_3$ with the help of 2D NMR double quantum correlation spectroscopy (gDQCOSY), total correlation

Scheme 1. Preparation of compounds **5**.



spectroscopy (TOCSY), and nuclear overhauser enhancement spectroscopy (NOESY) experiments. As a representative example, characteristic chemical shift difference between compound **8h** and **9h** in ^{1}H NMR is identified. The protons in compound **8h** show upfield shift of C_1H to C_{16}H and downfield shift of C_{11}H to C_{23}H, whereas in compound **9h** the chemical shift is reversed. Similarly, the change in chemical shift of compounds **8a** and **9a** are compared and found to be different. The comparative proton chemical shift (ppm) and coupling constant (J = Hz) for both the compounds are outlined in Table 3.

Thus, compound **8h** show the strong NOE correlations between C_{16}H/$C_{12}H_3$, C_{16}H/C_{18}H, and C_{18}H/C_{22}H, which provide compelling evidence for energy minimized structure shown in Figure 1. Similarly, compound **9h** show the strong NOE correlations between C_{16}H/C_1H (aromatic) and C_{16}H/C_{18}H, and C_{18}H/C_{22}H support the energy minimized structure as shown in Figure 2. In order to confirm the structure of aryl substituted derivatives, compounds **8a** and **9a** are also analyzed by ^{1}H NMR followed by NOE correlations, and the structures are established. The comparative proton chemical shift (ppm) and coupling constant (J = Hz) data for both the compounds and their NOE correlations are presented in the Experimental section. The strong NOE correlations of compound **8a** between protons of C_{21}H/C_{16}H, C_{21}H/C_{23}H, C_{23}H/C_{28}H, and C_{20}H/$C_{11}H_3$ (methyl) provide an emphatic support for the energy minimized structure shown in Figure 3. Similarly, in compound **9a** the strong NOE correlations between protons of C_{21}H/C_6H, C_{21}H/C_{26}H, and C_{20}H/

Scheme 2. Preparation of compounds **8** and **9**.

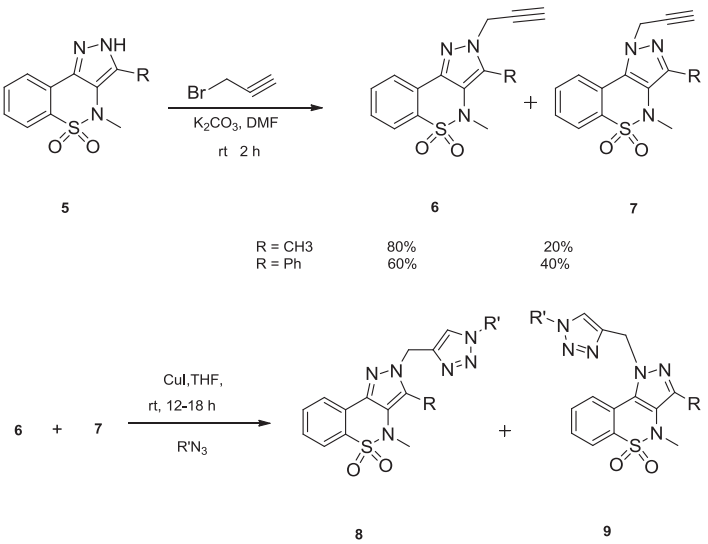


Table 1

Physical properties of compounds **5–7**.

S. no	Compounds	R	mp (°C)	Yield (%)
1	**5a**	CH_3	229–230	89
2	**5b**	C_6H_5	246–247	93
3	**6a + 7a**	CH_3	154–155	84 (67 + 17)
4	**6b + 7b**	C_6H_5	169–170	80 (48 + 32)

$C_{12}H_3$ (methyl) provide the clear-cut evidence for the structure outlined in Figure 4.

RESULTS AND DISCUSSION

***In vitro* antibacterial activity**. Compounds **8a–h** and **9a–h** were dissolved in DMSO and screened for *in vitro* antibacterial activity against Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*) and gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*) bacteria. The MIC values of the compounds were compared with those obtained with penicillin and streptomycin. However, none of the compounds showed significant activity against all species of Gram-positive and Gram-negative bacteria at 150-μg/mL concentration except compounds **9a** and **9g**, which showed response at 75-μg/mL concentration against *B. subtilis*. The details of the compounds and their activity profiles are tabulated in Table 4.

***In vitro* antifungal activity**. The fungal strains were obtained from the Institute of Microbial Technology, Chandigarh, India. The compounds **8a–h** and **9a–h** were screened *in vitro* against the fungal strains, viz. *Candida albicans* (MTCC 227), *Saccharomyces cerevisiae* (MTCC 36), *Aspergillus niger* (MTCC 1344), *Aspergillus flavus* (MTCC 277), and *Candida rugosa* (NCIM 3462) at 100- and 150-μg/mL concentrations by agar cup diffusion method. All the compounds were found to be inactive against all the strains except compounds **9a** and **9g**, which showed response at 75 μg/mL against *B. subtilis*.

Table 3

Chemical shift of protons in compounds **8h** and **9h**.

S. no	Protons	Chemical shift (ppm) of compounds **8h**	Chemical shift (ppm) of compounds **9h**
1	C_1H	7.98 (d, 1H, J = 7.8 Hz)	8.15 (d, 1H, J = 7.8 Hz)
2	C_2H	7.52 (t, 1H, J = 7.8 Hz)	7.59 (m, 1H)
3	C_3H	7.65 (t, 1H, J = 7.8 Hz)	7.74 (t, 1H, J = 7.8 Hz)
4	C_4H	7.92 (d, 1H, J = 7.8 Hz)	7.99 (d, 1H, J = 7.8 Hz)
5	$C_{11}H_3$	3.02 (s, 3H)	2.38 (s, 3H)
6	$C_{12}H_3$	2.44 (s, 3H)	3.03 (s, 3H)
7	$C_{16}H$	5.45 (s, 2H)	5.68 (s, 2H)
8	$C_{18}H$	7.59 (s, 1H)	7.59 (m, 1H)
9	$C_{22}H$	4.64 (m, 2H)	4.63 (m, 2H)
10	$C_{23}H$	2.82 (m, 2H)	2.78 (m, 2H)

Antioxidant activity. The compounds **6a + 7a**, **6b + 7b**, **8a–h**, and **9a–h** were screened *in vitro* for inhibition of pyrogallol auto-oxidation in alkaline solution as per reported procedure of S. Marklund and G. Marklund [25]. Compounds **8e**, **8g**, and **9f** showed good antioxidant activity at 50-μ*M* concentration and increased with increase in concentration. Compounds **9b** and **9c** showed high activity at 50-μ*M* concentration but decreased activity with increase in concentration. All other compounds promote pyrogallol auto-oxidation rather than inhibition and increase with increase in concentration. The mixture of compounds **6b + 7b** show maximum pyrogallol auto-oxidation inhibition activity at 100-μ*M* concentration. The structure activity relation reveals

Table 2

Physical properties of compounds **8a–h** and **9a–h**.

S. no	Compounds	R	R^1	Yield (%)	mp (°C)
1	**8a**	C_6H_5	3-$CF_3C_6H_4$	53	114–115
2	**9a**	C_6H_5	3-$CF_3C_6H_4$	35	134–135
3	**8b**	C_6H_5	C_6H_5	54	192–193
4	**9b**	C_6H_5	C_6H_5	36	132–133
5	**8c**	C_6H_5	$-(CH_2)_2-C_8F_{17}$	50	176–177
6	**9c**	C_6H_5	$-(CH_2)_2-C_8F_{17}$	34	145–146
7	**8d**	C_6H_5	$-(CH_2)_2-C_6F_{13}$	40	173–174
8	**9d**	C_6H_5	$-(CH_2)_2-C_6F_{13}$	26	128–129
9	**8e**	C_6H_5	$-(CH_2)_2-C_6H_{13}$	38	84–85
10	**9e**	C_6H_5	$-(CH_2)_2-C_6H_{13}$	25	82–83
11	**8f**	CH_3	C_6H_5	70	158–159
12	**9f**	CH_3	C_6H_5	18	196–197
13	**8g**	CH_3	3-$CF_3C_6H_4$	61	212–213
14	**9g**	CH_3	3-$CF_3C_6H_4$	15	90–91
15	**8h**	CH_3	$-(CH_2)_2-C_8F_{17}$	59	173–174
16	**9h**	CH_3	$-(CH_2)_2-C_8F_{17}$	14	110–111

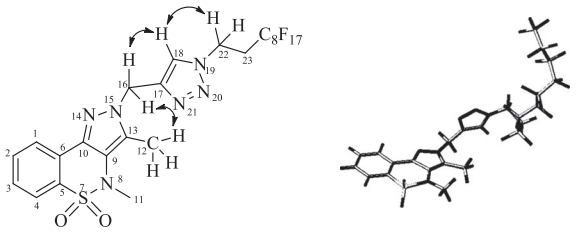


Figure 1. Compound **8h**.

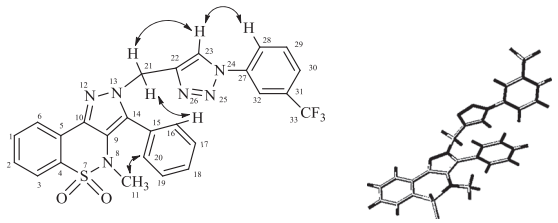


Figure 3. Compound **8a**.

that the activity of compounds is independent of triazole ring and the substituents therein. The details are tabulated in Table 5.

CONCLUSION

A series of novel triazole tagged pyrazole fused naphthalene 5-thiazine-5,5-dioxide derivatives **8** and **9** were prepared and screened for antimicrobial and antioxidant activities. Compounds **8e**, **8g**, and **9f** have been identified to show promising auto-oxidant activity.

EXPERIMENTAL

Melting points were recorded on Cassia-Siamia (VMP-AM) melting point apparatus and are uncorrected. All chemicals and reagents were purchased from Aldrich (Sigma-Aldrich, St. Louis, MO) and Merck (Darmstadt, Germany). IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. 1H NMR spectra were recorded on Bruker AV (Karlsruhe, Germany) 300 and 600MHz in CDCl3 and DMSO-d6 using TMS as internal standard. 13C NMR spectra were recorded on Bruker AV 75MHz in CDCl3 and DMSO-d6. Electron impact and chemical ionization mass spectra were recorded on a VG 7070H instrument at 70 eV. All the reactions were monitored by thin layer chromatography on precoated silica gel 60F254 (mesh); spots were visualized with UV light. Merck silica gel (60-120 mesh) was used for column chromatography.

1,1-Dioxo-2-(2-oxo-propyl)-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one (2a). See Ahmad et al. [19].

1,1-Dioxo-2-(2-oxo-2-phenyl-ethyl)-1,2-dihydro-1λ^6-benzo [d]isothiazol-3-one (2b). See Kim et al. [10,26].

1-(4-Hydroxy-1,1-dioxo-1,2-dihydro-1λ^6-benzo[e][1,2]thiazin-3-yl)-ethanone (3a). See Ahmad et al. [19].

(4-Hydroxy-1,1-dioxo-1,2-dihydro-1λ^6-benzo[e][1,2]thiazin-3-yl)-phenyl-methanone (3b). See Kim et al. [10,26].

1-(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-1λ^6-benzo[e] [1,2]thiazin-3-yl)-ethanone (4a). See Ahmad et al. [19].

(4-Hydroxy-2-methyl-1,1-dioxo-1,2-dihydro-1λ^6-benzo[e] [1,2]thiazin-3-yl)-phenyl-methanone (4b). See Ahmad et al. [19].

Preparation of 3,4-disubstituted-2,4-dihydropyrazolo[4,3-*c*] [1,2]benzothiazine-5,5-dioxide (5a–b): General procedure. A mixture of 1-(4-hydroxy-2-methyl-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl) ethanone/phenyl methanone (19.8 mmol) and hydrazine monohydrate (99.0 mmol) was added to ethanol (20 mL). The reaction mixture was refluxed for 2 h while stirring; unreacted hydrazine and ethanol were removed under vacuum. The residue obtained was poured into ice cold hydrochloric acid (20 mL, 10%); the precipitate obtained was filtered, washed with excess water and later with cold ethanol, and dried.

3,4-Dimethyl-2,4-dihydropyrazolo[4,3-c][1,2]benzothiazine-5,5-dioxide (5a). Light yellow powder, yield 89%, mp 229–230°C; IR (KBr) cm^{-1}: 3362, 1600, 1324, 1140; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 3.00 (s, 3H, NCH_3), 7.49–7.58 (m, 1H, ArH), 7.63–7.72 (m, 1H, ArH), 7.83 (d, J = 7.7 Hz, 1H, ArH), 7.97 (d, J = 7.7 Hz, 1H, ArH), 10.09 (brs, 1H, NH); MS *m/z*: 249.0 (M^+).

4-Methyl-3-phenyl-2,4-dihydropyrazolo[4,3-c][1,2]benzothiazine-5,5-dioxide (5b). White powder, yield 93%, mp 246–247°C ; IR (KBr) cm^{-1}: 3365, 1603, 1330, 1145; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.94 (s, 3H, NCH_3), 7.33–7.41 (m, 1H, ArH), 7.44–7.53 (m, 2H, ArH), 7.55–7.63 (m, 1H, ArH), 7.69–7.77 (m, 1H, ArH), 7.86–7.91 (m, 1H, ArH), 7.93–8.00 (m, 2H, ArH), 8.03–8.08 (m, 1H, ArH); MS *m/z*: 311.0 (M^+).

Preparation of 3,4-dimethyl-1-prop-2-ynyl-1,4-dihydro-5-thia-1,2,4-triazocyclopenta[*a*]naphthalene-5,5-dioxide (6a) and 3,4-dimethyl-2-prop-2-ynyl-2,4-dihydro-5-thia-1,2,4-triazacyclopenta[*a*]naphthalene-5,5-dioxide (7a)

Procedure. A mixture of 3,4-dimethyl-2,4-dihydro pyrazolo[4,3-*c*][1,2]benzothiazine-5,5-dioxide **5a** (5.0 g, 20.0 mmol), anhydrous potassium carbonate (3.31 g, 24.0 mmol), and dry DMF (30 mL) was stirred for a period of 30 min at room temperature followed by the addition of propargyl bromide (3.55 mL, 40.0 mmol). The total reaction mixture was stirred for a period of 12 h at room temperature and then poured over ice water, and precipitate

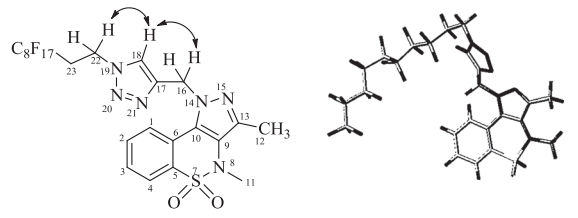


Figure 2. Compound **9h**.

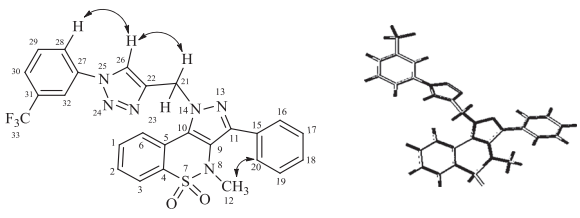


Figure 4. Compound **9a**.

Table 4

Antibacterial activity of compounds **6a + 7a**, **6b + 7b**, **8a–h**, and **9a–h**.

	MIC (μg/mL)				
Compound	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeroginosa*
6a + 7a	>150	>150	>150	>150	>150
6b + 7b	150	>150	>150	>150	>150
8a	>150	>150	>150	>150	>150
8b	>150	>150	>150	>150	>150
8c	75	>150	>150	>150	>150
8d	150	>150	>150	>150	>150
8e	>150	>150	>150	>150	>150
8f	150	>150	>150	>150	>150
8g	>150	>150	>150	>150	>150
8h	>150	>150	>150	>150	>150
9a	75	>150	>150	>150	>150
9b	150	>150	>150	>150	>150
9c	150	>150	>150	>150	>150
9d	>150	>150	>150	>150	>150
9e	>150	>150	>150	>150	>150
9f	>150	>150	>150	>150	150
9 g	75	>150	>150	>150	>150
9 h	>150	>150	>150	>150	>150
Penicillin	**1.562**	**1.562**	**3.125**	**12.5**	**12.5**

thus obtained was washed with excess water and dried. Light yellowish powder, yield 84%; mp 154–156°C.

3,4-Dimethyl-1-prop-2-ynyl-1,4-dihydro-5-thia-1,2,4-triazacyclopenta[a]naphthalene-5,5-dioxide (6a). IR (KBr) cm^{-1} : 2117 (—C≡C), 1594 (CN), 1342 (SO_2asym), 1171 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.41–2.44 (m, 1H, —C≡CH), 2.46 (s, 3H, CH_3), 3.03 (s, 3H, NCH_3), 4.92 (d, $J = 2.6$ Hz, 2H, NCH_2), 7.47–7.55 (m, 1H, ArH), 7.61–7.68 (m, 1H, ArH), 7.89 (d, $J = 7.7$ Hz, 1H, ArH,), 7.98 (d, $J = 7.7$ Hz, 1H, ArH); MS *m/z*: 287.0 (M^+).

3,4-Dimethyl-2-prop-2-ynyl-2,4-dihydro-5-thia-1,2,4-triazacyclopenta[a]naphthalene-5,5-dioxide (7a). IR (KBr) cm^{-1}: 2115 (—C≡C), 1594 (—CN), 1314 (SO_2asym), 1170 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.53 (m, 1H, —C≡CH), 3.07 (s, 3H, NCH_3), 5.09 (d, $J = 2.4$ Hz, 2H, NCH_2), 7.56–7.60 (m, 1H, ArH), 7.70–7.77 (m, 1H, ArH), 7.94 (d, $J = 7.7$ Hz, 1H, ArH), 8.01 (d, $J = 7.7$ Hz, 1H, ArH); ESI–MS (*m/z*): 287.0 (M^+).

Preparation of 2-ethynyl-4-methyl-3-phenyl-2,4-dihydro-5-thia-1,2,4-triazocyclopenta[*a*]naphthalene-5,5-dioxide (6b) and 1-ethynyl-4-methyl-3-phenyl-1,4-dihydro-5-thia-1,2,4-triazacyclopenta[*a*]naphthalene-5,5-dioxide (7b).

Procedure. A mixture of 4-methyl-3-phenyl-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[*a*]naphthalene **5b** (5.0 g, 16.07 mmol), anhydrous potassium carbonate (3.31 g, 24.0 mmol), and dry DMF (30 mL) was stirred for a period of 30 min at room temperature followed by the addition of propargyl bromide (2.84 mL, 32 mmol). Then, this total reaction mixture was stirred for a period of 12 h at room temperature and then poured over ice water, and precipitate thus obtained was washed with excess water and dried. Light yellowish powder, yield 84%; mp 169–170°C.

2-Ethynyl-4-methyl-3-phenyl-2,4-dihydro-5-thia-1,2,4-triazacyclopenta[a]naphthalene-5,5-dioxide (6b). IR (KBr) cm^{-1}: 2114 (—C≡C), 1594 (CN), 1343 (SO_2asym), 1175 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (t, $J = 2.2$ Hz, 1H, —C≡CH), 2.82 (s, 3H, NCH_3), 4.89 (d, $J = 2.2$ Hz, 1H, NCH_2), 7.32–7.51 (m, 4H, ArH), 7.63–7.72 (m, 3H, ArH), 7.99–8.06 (m, 2H, ArH); ESI–MS (*m/z*): 349.0 (M^+).

Table 5

Percent of pyrogallol auto-oxidation inhibition.

		% of pyrogallol auto-oxidation inhibition	
S. no	Compound	50 μ*M*	100 μ*M*
1	**6a + 7a**	7.17	6.51
2	**6b + 7b**	11.01	51.76
3	**8a**	−8.09	−10.79
4	**8b**	−7.63	−17.55
5	**8c**	6.04	6.43
6	**8d**	5.57	1.25
7	**8e**	7.20	36.32
8	**8f**	8.24	−9.66
9	**8g**	10.68	25.51
10	**8h**	−2.31	−5.99
11	**9a**	−33.91	−47.30
12	**9b**	18.53	−12.95
13	**9c**	9.30	2.25
14	**9d**	−14.44	−38.39
15	**9e**	−5.11	16.43
16	**9f**	10.99	19.08
17	**9g**	−40.63	−89.84
18	**9h**	−6.94	−19.75

1-Ethynyl-4-methyl-3-phenyl-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (7b). IR (KBr) cm^{-1}: 2117 (—C≡C), 1594 (CN), 1343 (SO_2asym), 1175 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.59 (t, J = 2.2 Hz, 1H, —C≡CH), 2.96 (s, 3H, NCH_3), 5.21 (d, J = 2.2 Hz, 1H, NCH_2), 7.41–7.60 (m, 4H, ArH), 7.69–7.80 (m, 2H, ArH), 8.00–8.12 (m, 3H, ArH); MS *m/z*: 349.0 (M^+).

Preparation of triazole tagged pyrazole fused naphthalene-5,5-dioxide derivatives 8a–h and 9a–h: General procedure. A mixture of propargylated products **6** and **7** (0.2 g) and catalytic amount of CuI was taken into a 50-mL two-necked RB flask, and then dry THF was added under inert condition. The reaction mixture was stirred for 30 min at room temperature, and then alkyl azide was added to the reaction mixture and further stirred at room temperature till the reaction was completed (12–18 h). Then, the crude product was purified by passing through a column packed with silica gel and *n*-hexane:ethylacetate (4:1) as eluents.

4-Methyl-3-phenyl-2-[1-(3-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-2,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (8a) Light yellow powder; mp 114–115°C; IR (KBr) cm^{-1}: 1599 (—CN), 1349 (SO_2asym), 1182 (SO_2sym); ^1H NMR (600 MHz, $CDCl_3$): δ 2.95 (s, 3H, NCH_3), 5.89 (s, 2H, NCH_2), 7.41 (t, *J* = 7.6 Hz, 1H, ArH), 7.48 (t, *J* = 7.6 Hz, 2H, ArH,), 7.64–7.66 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.81 (t, *J* = 7.8 Hz, 1H, ArH), 7.90 (d, *J* = 7.8 Hz, 1H, ArH), 8.01–8.05 (m, 4H, ArH), 8.06 (s, 1H, ArH), 8.27 (d, *J* = 7.6 Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{26}H_{19}F_3N_6SO_2$ ($[M + Na]^+$): 559.1140, found 559.1161.

4-Methyl-3-phenyl-1-[1-(3-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (9a) Yellowish powder; mp 134–135°C; IR (KBr) cm^{-1}: 1600 (—CN), 1323 (SO_2asym), 1165 (SO_2sym); ^1H NMR (600 MHz, $CDCl_3$): δ 2.82 (s, 3H, NCH_3), 5.56 (s, 2H, NCH_2), 7.51–7.59 (m, 4H, ArH), 7.69 (t, *J* = 7.8 Hz, 2H, ArH), 7.73–7.76 (m, 3H, ArH), 7.94–7.96 (m, 2H, ArH), 8.04 (s, 1H, ArH), 8.08 (d, *J* = 7.8 Hz, 1H, ArH), 8.12 (s, 1H, triazole H); HRMS *m/z* Calcd for $C_{26}H_{19}F_3N_6SO_2$ ($[M + Na]^+$): 559.1140, found 559.1147.

4-Methyl-3-phenyl-2-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-2,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (8b). White powder; mp 192–193°C; IR (KBr) cm^{-1}: 1594 (—CN), 1342 (SO_2asym), 1181 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.94 (s, 3H, NCH_3), 5.85 (s, 2H, NCH_2), 7.34–7.53 (m, 6H, ArH), 7.59–7.66 (m, 1H, ArH), 7.70–7.74 (m, 2H, ArH), 7.78–7.85 (m, 1H, ArH), 7.99–8.06 (m, 4H, ArH), 8.32–8.36 (m, 1H, ArH); HRMS *m/z* Calcd for $C_{26}H_{20}N_6SO_2$ ($[M + H]^+$): 469.1446, found 469.1444.

4-Methyl-3-phenyl-1-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (9b). Light yellow powder; mp 132–133°C; IR (KBr) cm^{-1}: 1598 (—CN), 1341 (SO_2asym), 1147 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.80 (s, 3H, ArH), 7.47–7.68 (m, 7H, ArH), 7.72–7.83 (m, 4H, ArH), 7.91 (d, *J* = 7.7 Hz, 1H, ArH), 8.04 (d, *J* = 7.7 Hz, 1H, ArH), 8.09 (s, 1H, triazol H); HRMS *m/z* Calcd for $C_{26}H_{20}N_6SO_2$ ($[M + Na]^+$): 491.1266, found 491.1268.

2-[1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadeca-fluoro-decyl)-1H-[1,2,3]triazol-4-ylmethyl]-4-methyl-3-phenyl-2,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (8c). White powder; mp 176–177°C; IR (KBr) cm^{-1}: 1604 (—CN), 1342 (SO_2asym), 1149 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.68–2.87 (m, 2H, CH_2CF_2), 2.93 (s, 3H, NCH_3), 4.62 (t, *J* = 7.5 Hz, 2H, $N\underline{CH_2}CH_2$), 5.78 (s, 2H, NCH_2), 7.33–7.41 (m, 1H, ArH), 7.43–7.48 (m, 2H, ArH), 7.57–7.63 (m, 2H, ArH), 7.75–7.80 (m, 1H, ArH), 7.98–8.03 (m, 3H, ArH), 8.20 (d, *J* = 8.3 Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{29}H_{19}F_{17}N_6SO_2$ ($[M + Na]^+$): 861.0916, found 861.0874.

1-[1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadeca-fluoro-decyl)-1H-[1,2,3]triazol-4-ylmethyl]-4-methyl-3-phenyl-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (9c). White powder; mp 145–146°C; IR (KBr) cm^{-1}: 1602 (—CN), 1343 (SO_2asym), 1154 (SO_2sym); ^1HNMR (300 MHz, $CDCl_3$): δ 2.70–2.95 (m, 5H, CH_2CF_2 and NCH_3), 4.64 (t, *J* = 6.9 Hz, 2H, NCH_2CH_2), 5.43 (s, 2H, NCH_2), 7.43–7.78 (m, 8H, ArH), 7.91 (d, *J* = 7.3 Hz, 1H, ArH), 8.01 (d, *J* = 7.3 Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{29}H_{19}F_{17}N_6SO_2$ ($[M + Na]^+$): 861.0916, found 861.0912.

4-Methyl-3-phenyl-2-[1-(3,3,4,4,5,5,6,6,7,7,8,8,8-trideca-fluoro-octyl)-1H-[1,2,3]triazol-4-ylmethyl]-2,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (8d). White powder; mp 173–174°C; IR (KBr) cm^{-1}: 1602 (—CN), 1341 (SO_2asym), 1187 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.68–2.87 (m, 2H, $\underline{CH_2}CF_2$), 2.92 (s, 3H, NCH_3), 4.62 (t, *J* = 7.5 Hz, 2H, $N\underline{CH_2}CH_2$), 5.77 (s, 2H, NCH_2), 7.33–7.40 (m, 1H, ArH), 7.41–7.49 (m, 2H, ArH), 7.57–7.64 (m, 2H, ArH), 7.74–7.81 (m, 1H, ArH), 7.97–8.05 (m, 3H, ArH), 8.20 (d, *J* = 8.3 Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{27}H_{19}F_{13}N_6SO_2$ ($[M + H]^+$): 739.1160, found 739.1173.

4-Methyl-3-phenyl-1-[1-(3,3,4,4,5,5,6,6,7,7,8,8,8-trideca-fluoro-octyl)-1H-[1,2,3]triazol-4-ylmethyl]--1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (9d). Yellowish powder; mp 128–129°C; IR (KBr) cm^{-1}: 1603 (—CN), 1346 (SO_2asym), 1146 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.70–2.94 (m, 5H, $\underline{CH_2}CF_2$ and NCH_3), 4.66 (t, *J* = 7.5 Hz, 2H, $N\underline{CH_2}CH_2$), 5.43 (s, 2H, NCH_2), 7.46–7.78 (m, 8H, ArH), 7.92 (d, *J* = 7.5 Hz, 1H, ArH), 8.02 (d, *J* = 7.5 Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{27}H_{19}F_{13}N_6SO_2$ ($[M + Na]^+$): 761.0980, found 761.1009.

4-Methyl-2-(1-octyl-1H-[1,2,3]triazol-4-ylmethyl)-3-phenyl-2,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (8e). Brown solid; mp 84–85°C; IR (KBr) cm^{-1}: 1600 (—CN), 1343 (SO_2asym), 1186 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 0.8–0.94 (m, 3H, $CH_2\underline{CH_3}$), 1.1–1.36 (m, 10H, C_5H_{10}), 1.78–1.93 (m, 2H, $NCH_2\underline{CH_2}$), 2.93 (s, 3H, NCH_3), 4.3 (t, *J* = 6.7 Hz, 2H, $N\underline{CH_2}CH_2$), 5.77 (s, 2H, NCH_2), 7.32–7.41 (m, 1H, ArH), 7.96–8.07 (m, 3H, ArH),

8.28 (d, $J = 8.3$ Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{27}H_{32}N_6SO_2$ ($[M + H]^+$): 505.0759, found 505.0773.

4-Methyl-1-(1-octyl-1H-[1,2,3]triazol-4-ylmethyl)-3-phenyl-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (9e). Brown solid; mp 82–83°C; IR (KBr) cm^{-1}: 1603 (—CN), 1340 (SO_2asym), 1140 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 0.79–0.95 (m, 3H, $CH_2\underline{CH_3}$), 1.15–1.41 (m, 10H, C_5H_{10}), 1.82–1.97 (m, 2H, $NCH_2\underline{CH_2}$), 2.79 (s, 3H, NCH_3), 4.25–4.40 (t, 2H, $N\underline{CH_2}CH_2$), 5.42 (s, 2H, NCH_2), 7.42–7.67 (m, 6H, ArH), 7.70–7.82 (m, 2H, ArH), 7.86–7.96 (m, 1H, ArH). 7.97–8.07 (m, 1H, ArH); HRMS *m/z* Calcd for $C_{27}H_{32}N_6SO_2$ ($[M + H]^+$): 505.0759, found 505.0782.

3,4-Dimethyl-2-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-2,4-dihydro-5-thia-1,2,4-triaza-cyclo penta[a]naphthalene-5,5-dioxide (8f). Yellowish powder; mp 158–159°C; IR (KBr) cm^{-1}: 1603 (—CN), 1348 (SO_2asym), 1170 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.5 (s, 3H, CH_3), 3.01 (s, 3H, NCH_3), 5.50 (s, 2H, NCH_2), 7.36–7.43 (m, 1H, ArH), 7.45–7.55 (m, 3H, ArH), 7.60–7.67 (m, 1H, ArH), 7.68–7.74 (d, $J = 7.5$ Hz, 2H, ArH,), 7.87–7.92 (d, $J = 7.5$ Hz, 1H, ArH), 7.94–8.00 (m, 2H, ArH); HRMS *m/z* Calcd for $C_{20}H_{18}N_6SO_2$ ($[M + Na]^+$): 429.1109, found 429.1111.

3,4-Dimethyl-1-(1-phenyl-1H-[1,2,3]triazol-4-ylmethyl)-1,4-dihydro-5-thia-1,2,4-triaza-cyclo penta[a]naphthalene-5,5-dioxide (9f). Light yellow powder; mp 196–197°C; IR (KBr) cm^{-1}: 1594 (—CN), 1343 (SO_2asym), 1171 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 5.72 (s, 2H, NCH_2), 7.36–7.55 (m, 3H, ArH), 7.60 (t, $J = 7.5$ Hz, 1H, ArH), 7.71 (d, $J = 7.7$ Hz, 2H, ArH,), 7.80 (t, $J = 7.7$ Hz, 1H, ArH), 7.94–8.01 (m, 2H, ArH), 8.29 (d, $J = 7.7$ Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{20}H_{18}N_6SO_2$ ($[M + Na]^+$): 429.1109, found 429.1118.

3,4-Dimethyl-2-[1-(3-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-2,4-dihydro-5-thia-1,2,4-triaza-cyclo-penta[a] naphthalene-5,5-dioxide (8g). White powder; mp 212–213°C; IR (KBr) cm^{-1}: 1594 (—CN), 1328 (SO_2asym), 1166 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 5.51 (s, 2H, NCH_2), 7.48–7.51 (m, 1H, ArH), 7.60–7.74 (m, 3H, ArH), 7.87–8.07 (m, 5H, ArH); HRMS *m/z* Calcd for $C_{21}H_{17}F_3N_6SO_2$ ($[M + Na]^+$): 497.0983, found 497.0992.

3,4-Dimethyl-1-[1-(3-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethyl]-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a] naphthalene-5,5-dioxide (9g). Light yellow powder; mp 90–91°C; IR (KBr) cm^{-1}: 1599 (—CN), 1334 (SO_2asym), 1175 (SO_2sym); ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3), 3.04 (s, 3H, NCH_3), 5.75 (s, 2H, NCH_2), 7.56–7.72 (m, 3H, ArH), 7.74–7.83 (m, 1H, ArH), 7.74–7.83 (m, 1H, ArH), 7.89–8.05 (m, 4H, ArH), 8.22 (d, $J = 8.31$ Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{21}H_{17}F_3N_6SO_2$ ($[M + Na]^+$): 497.0983, found 497.0999.

2-[1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadeca-fluoro-decyl)-1H-[1,2,3]triazol-4-yl methyl]-3,4-dimethyl-2,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (8h). White powder mp 173–174°C; IR (KBr) cm^{-1}: 1598 (—CN), 1341 (SO_2asym), 1149 (SO_2sym); ^1H NMR (600 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 2.74–2.90 (m, 2H, CH_2CF_2), 3.02 (s, 3H, NCH_3), 4.64 (m, 2H, $N\underline{CH_2}CH_2$), 5.45 (s, 2H, NCH_2), 7.52 (t, $J = 7.8$ Hz, 1H, ArH), 7.59 (s, 1H, ArH), 7.65 (t, $J = 7.8$ Hz, 1H, ArH), 7.92 (d, $J = 7.8$ Hz, 1H, ArH), 7.98 (d, $J = 7.8$ Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{24}H_{17}F_{17}N_6SO_2$ ($[M + Na]^+$): 799.0759, found 799.0773.

1-[1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro-decyl)-1H-[1,2,3]triazol-4-ylmethyl]-3,4-dimethyl-1,4-dihydro-5-thia-1,2,4-triaza-cyclopenta[a]naphthalene-5,5-dioxide (9h). Yellowish powder; mp 110–111°C; IR (KBr) cm^{-1}: 1599 (—CN), 1346 (SO_2asym), 1149 (SO_2sym); ^1H NMR (600 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 2.70–2.86 (m, 2H, CH_2CF_2), 3.03 (s, 3H, NCH_3), 4.62–4.64 (m, 2H, $N\underline{CH_2}CH_2$), 5.68 (s, 2H, NCH_2), 7.52–7.61 (m, 2H, ArH), 7.74 (t, $J = 7.8$ Hz, 1H, ArH), 7.99 (d, $J = 7.8$ Hz, 1H, ArH), 8.15 (d, $J = 7.8$ Hz, 1H, ArH); HRMS *m/z* Calcd for $C_{24}H_{17}F_{17}N_6SO_2$ ($[M + Na]^+$): 799.0759, found 799.0780.

Antibacterial activity: Procedure. Five bacterial test organisms such as *B. subtilis* (MTCC 441), *S. aureus* (MTCC 96), *S. epidermidis* (MTCC 435), *E. coli* (MTCC 443), and *P. aeruginosa* (MTCC 741) were selected and obtained from the Institute of Microbial Technology, Chandigarh, India. Cultures of test organisms were maintained on Nutrient agar slants and were subcultured in Petri dishes prior to testing. The media used was Nutrient agar, Nutrient broth procured from Himedia Laboratories, Mumbai, India. The minimum inhibitory concentration was determined by broth dilution method.

Antifungal activity: Procedure. Antifungal activity was studied by agar cup diffusion method. The readymade potato dextrose agar medium (Himedia, 39 g) was suspended in distilled water (1000 mL) and heated to boiling until it dissolved completely. The medium and Petri dishes were autoclaved at a pressure of 15 lb/inch for 20 min. Agar cup bioassay was employed for testing antifungal activity. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in acetone, and different concentrations (30 and 100 μg/mL) were made. After inoculation, cups were scooped out with a 6-mm sterile cork borer, and the lids of the dishes were replaced. To each cup, different concentrations (30 and 100 μg/mL) of test solutions were added. Controls were maintained with acetone and amphotericin-B (50 μg/mL). The treated and

the controls were kept at 28°C for 48 h. Inhibition zones were measured, and the diameter was calculated in millimeter.

Antioxidant activity: Procedure. Compounds **8a–h**, **9a–h**, **6a + 7a**, and **6b + 7b** were dissolved in DMSO solution to prepare 100 m*M* stock solutions. Potassium phosphate buffer (50 m*M*; pH 8.0) containing 1 m*M* EDTA was used as assay buffer. Total reaction volume of the assay was 200 μL, which contained various concentrations of the test compounds (0–100 μ*M*), and was studied for their ability to inhibit the pyrogallol auto-oxidation at 420 nm for using TECAN M-200 multimode reader. The readings were taken at 1-min interval up to 5 min. DMSO solution was used as a reagent blank. All the experiments were carried out in triplicates, and average value is taken for consideration.

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