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FACILE $TiCl_4$-CATALYZED SYNTHESIS OF NOVEL 1,2,4-TRIAZOLES APPENDED TO THIAZOLES

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The reaction of sydnone-derived 3-aryl-5-methyl-1,3,4-oxadiazol-2(3H)-ones with thiourea and α-bromoacetophenone derivatives in the presence of a catalytic amount of $TiCl_4$ produces 2-aryl-4-(4-aryl-1,3-thiazol-2-yl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-ones. The title compounds were screened for their antibacterial and antifungal activity. The toxicity of the compounds was evaluated in terms of mutagenicity, tumorigenicity, and reproductive effects. The drug-relevant properties (ClogP, drug-likeness, and drug score) were calculated, and the structure–activity relationship was discussed.

Keywords: mesoionic compounds, sydnones, $TiCl_4$, 1,3-dipolar cycloaddition.

Sydnone is a typical mesoionic compound which has been investigated extensively because of its unique electronic structure and biological activity. Sydnone has also recently gained importance as it readily undergoes ring transformation into various heterocycles by 1,3-dipolar cycloaddition [1–3].

The importance of 1,2,4-triazoles in organic synthesis is due to the wide range of their biological properties, such as antibacterial, antimycobacterial, antimycotic, antidepressant, cardiotonic, analgesic, and anti-inflammatory activities [4–13]. Thiazole derivatives are known to possess anti-inflammatory, anticancer, antibacterial, antifungal, and antiallergic activities [14–19].

Many procedures for the synthesis of 4-substituted 1,2,4-triazoles have been described, such as the reaction of ethyl formate or formic acid with hydrazine hydrate [20, 21], and the reaction of carbon monoxide with hydrazine hydrate under high pressure [22], and the reaction of an appropriate aliphatic, aromatic, or heterocyclic primary amine with diformohydrazide [23]. Another approach reported involves the reaction of diphenylformamidine with formohydrazide [24]. As an example of recyclization, 2-phenyl-4-phenyl-azooxazolin-5-one upon treatment with alcoholic potassium hydroxide gave 1,5-diphenyl-1*H*-1,2,4-triazol-3-ylcarboxylic acid in quantitative yield [25]. 1,2-Dihydro-1,2,4,5-tetrazines undergo isomerization to 1,2,4-triazole derivatives [26]. We were interested to find mild conditions for 1,2,4-triazole synthesis, possibly facilitated by a catalyst. The use of titanium(IV) chloride, an acidic catalyst, has been explored for various

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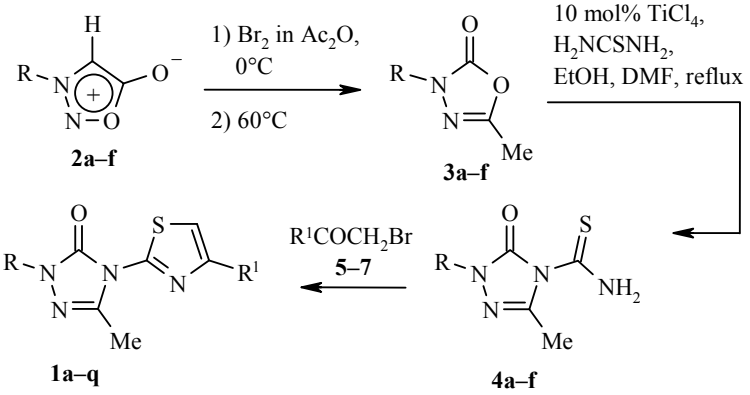
organic transformations, such as synthesis of α-aminophosphonates [27], Biginelli reaction [28], olefination of aldehydes [29], and synthesis of imidazo[1,2-*a*]pyridine derivatives [30]. In this communication, we wish to report the use of $TiCl_4$ as a mild, efficient, and commercially available catalyst for the synthesis of 2-aryl-4-(4-aryl-1,3-thiazol-2-yl)-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones **1a**–**q** (Scheme 1).

Scheme 1



1 a R = Ph, R^1 = Ph, **b** R = *p*-MeC_6H_4, R^1 = Ph, **c** R = *m*-MeC_6H_4, R^1 = Ph, **d** R = *p*-ClC_6H_4, R^1 = Ph, **e** R = *m*-ClC_6H_4, R^1 = Ph, **f** R = Ph, R^1 = *p*-$O_2NC_6H_4$, **g** R = *p*-MeC_6H_4, R^1 = *p*-$O_2NC_6H_4$, **h** R = *m*-MeC_6H_4, R^1 = *p*-$O_2NC_6H_4$, **i** R = *p*-anisyl, R^1 = *p*-$O_2NC_6H_4$, **j** R = *p*-ClC_6H_4, R^1 = *p*-$O_2NC_6H_4$, **k** R = *m*-ClC_6H_4, R^1 = *p*-$O_2NC_6H_4$, **l** R = Ph, R^1 = *p*-BrC_6H_4, **m** R = *p*-MeC_6H_4, R^1 = *p*-BrC_6H_4, **n** R = *m*-MeC_6H_4, R^1 = *p*-BrC_6H_4, **o** R = *p*-anisyl, R^1 = *p*-BrC_6H_4, **p** R = *p*-ClC_6H_4, R^1 = *p*-BrC_6H_4, **q** R = *m*-ClC_6H_4, R^1 = *p*-BrC_6H_4;
2–4 a R = Ph, **b** R = *p*-MeC_6H_4, **c** R = *m*-MeC_6H_4, **d** R = *p*-ClC_6H_4, **e** R = *m*-ClC_6H_4, **f** R = *p*-anisyl;
5 R^1 = Ph; **6** R^1 = *p*-$O_2NC_6H_4$; **7** R^1 = *p*-BrC_6H_4

The strategy of the present investigation was based on the literature precedents where a combination of ring systems with pharmacologically active heterocycles results in molecules with better drug potential. In the light of these observations we have designed and synthesized molecules **1a**–**q** containing heterocycles of these classes.

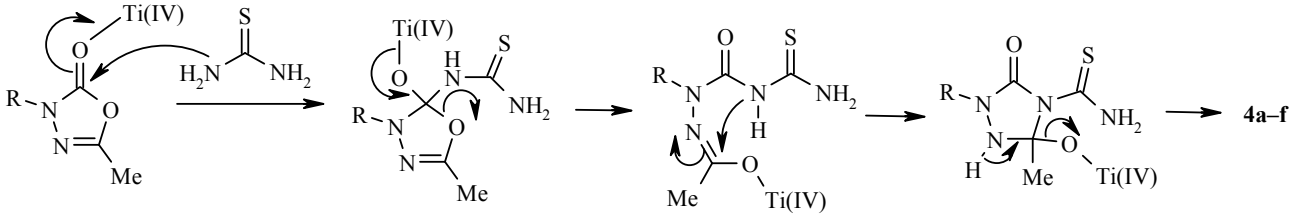
The 3-arylsydnones **2a**–**f** were the synthetic precursors which reacted with bromine in acetic anhydride [31] to form 1,3,4-oxadiazoles **3a**–**f**. Initially, allowing compound **3a** to react with thiourea in ethanol in the absence of the catalyst produced only 20% of compound **4a** after 24 h under reflux conditions. When a catalytic amount of $TiCl_4$ (5 mol %) was added, 60% conversion of compound **3a** to **4a** was observed after 5 h of reflux. Increasing the amount of $TiCl_4$ from 5 to 10 mol% resulted in 89% conversion after 2 h of reflux. Compound **1a** was obtained by cyclization of compound **4a** with α-bromoacetophenone (**5**) in a good yield. We tried to use also other Lewis acid catalysts like $MgBr_2$, $ZnCl_2$, I_2, VCl_3, sulfamic acid, and *p*-toluenesulfonic acid (PTSA) for the above conversion and observed lower yields than with $TiCl_4$ (Table 1).

TABLE 1. Comparison of Efficiency of Various Lewis Acid Catalysts on the Conversion of Compound **3a** into **1a** *via* Intermediate **4a**

Lewis acid catalyst	Time, h	Yield, %	Lewis acid catalyst	Time, h	Yield, %
$TiCl_4$	1	91	VCl_3	5	65
$MgBr_2$	10	50	Sulfamic acid	10	40
$ZnCl_2$	8	55	PTSA	6	50
I_2	7	53			

Having thus demonstrated $TiCl_4$ to be the most effective catalyst for the above conversion, we applied it to the reaction of compound **3a** with thiourea in the presence of (10 mol% $TiCl_4$, 2 h reflux). After completion of the reaction (monitored by TLC) and without the isolation of the intermediate **4a**, bromoacetophenone **5** was added to the reaction mixture. As a result, the title compound **1a** was produced in 87% yield. The plausible reaction mechanism is presented in Scheme 2. As the reaction is carried out in ethanol–DMF, $TiCl_4$ is likely converted into $Ti(OEt)_4$ that may also act as Lewis acid catalyst.

Scheme 2



Having established the best reaction conditions, we applied them to the reaction of compounds **3b–f** with thiourea in the presence of $TiCl_4$ followed by addition of substituted bromoacetophenones **5–7** *in situ*, furnishing the corresponding products **1b–q** in excellent yields.

The intermediate **4a** was isolated and characterized by IR, ^1H and ^{13}C NMR spectra. Its precursor **3a** has the C=O absorption band at 1770–1775 cm^{-1} in its IR spectrum [31]. The low-frequency shift of this band to 1707 cm^{-1} in compound **4a** indicates the replacement of oxygen atom by nitrogen in the heterocyclic ring. The presence of an NH_2 group in the compound **4a** is indicated by two IR absorption bands around 3327 and 3444 cm^{-1} and by a broad singlet at 2.03 ppm, suppressed by D_2O, in its ^1H NMR spectrum. Aromatic protons appeared in the range of 7.27–8.03 ppm as a multiplet.

The IR spectra of the title compounds **1a–q** showed a sharp band around 1710–1715 cm^{-1} due to the carbonyl group of the 1,2,4-triazole ring. In the ^1H NMR spectra, the closure of another heterocyclic ring was indicated by a singlet in the range of 6.5–6.7 ppm, ascribed to the thiazole proton at position 5. The ^{13}C NMR and mass spectra of compounds **1a–q** were consistent with the expected number of carbon atoms and molecular mass, respectively.

The antibacterial screening (Table 2) shows that compound **1a** without any substituent on the two phenyl rings and compounds with methyl (at the *meta* position, **1c**), as well as chloro and bromo (**1d**,**e**,**l**, and **1p**) substituents are active against *Escherichia coli* and *Bacillus cereus*, their activity being equal to or more than that of the reference drug Norfloxacin. This activity was found to vary with the substitution at the phenyl rings attached to the triazole and thiazole ring. The compounds having nitro group on the phenyl ring attached to the thiazole moiety show weak to moderate activity.

In the case of antifungal activity studies, compounds with *m*-tolyl (**1c**), *p*-bromophenyl (**1l**), and both *p*-chloro- and -bromophenyl substituents show activity higher than the reference drug Griseofulvin against the fungus *Candida albicans*. Also the assay against *Rhizoctonia bataticola* indicated that the compounds with the same set of substituents (**1a–c**,**l**,**o**,**p**) are more active than the reference drug. Interestingly, compounds **1f**,**g**,**j** with the nitro substituent show weak to moderate activity.

In view of the need to rapidly improve the lead structures into drug candidates, drug-likeness and toxicology parameters based on topological descriptors have gained considerable attention. For a compound to qualify as a drug candidate, certain parameters are to be analyzed according to Lipinski's rule of five [32]. The prediction of toxicity, drug-likeness, and drug score of the compounds was done using the on-line OSIRIS Property Explorer and the occurrence frequency of each fragment is determined within the collection of

TABLE 2. Antibacterial and Antifungal Activity, Toxicity, Drug-likeness, and Drug Score of the Title Compounds **1a–q***

Com-pound*[2]	*E. coli*		*B. cereus*		*A. candida*		*R. bataticola*		Clog P	Mol. wt.	Drug-likeness	Drug score
	Zone of inhibition, mm	RI, %	Zone of inhibition, mm	RI, %	Zone of inhibition, mm	RI, %	Zone of inhibition, mm	RI, %				
1a	95.00	99.95	91.00	**112.76**	79.00	**98.00**	72.00	**103.18**	**4.27**	334	**4.98**	**0.42**
1b	92.00	96.24	74.00	88.49	72.00	88.52	72.50	**104.04**	**4.76**	348	2.93	**0.36**
1c	97.00	**102.41**	83.00	**101.34**	98.00	**125.64**	84.00	**123.81**	**4.76**	348	**4.15**	**0.37**
1d	96.00	**101.18**	91.00	**112.76**	79.30	**98.94**	69.05	**98.10**	4.98	368	**4.89**	**0.32**
1e	94.50	99.83	89.00	**109.90**	72.00	88.52	65.50	92.00	4.98	368	**4.51**	**0.32**
1f	65.40	62.93	70.54	83.55	58.40	69.10	59.00	80.82	**4.02**	374	0.50	**0.30**
1g	65.00	62.93	74.00	88.49	42.00	45.68	65.00	91.14	**4.51**	388	-1.55	0.20
1h	57.00	53.06	67.00	78.50	40.00	42.83	64.00	89.42	**4.52**	388	-0.27	0.24
1i	86.00	88.84	79.00	95.63	63.00	75.67	58.40	79.79	**4.39**	404	-1.53	0.13
1j	76.00	76.50	68.00	79.93	74.00	91.37	42.00	51.59	**4.73**	415	0.41	0.24
1k	74.00	74.03	76.40	91.92	64.00	77.09	40.00	48.15	**4.73**	415	0.08	0.22
1l	94.50	99.33	83.00	**101.34**	98.00	**125.64**	74.00	**106.62**	5.13	412	**3.08**	**0.29**
1m	65.00	62.93	79.00	95.63	42.00	45.68	40.00	48.15	5.63	426	1.04	0.23
1n	86.00	88.84	68.00	79.93	65.50	79.24	42.00	51.59	5.63	426	2.30	0.25
1o	57.00	53.06	60.00	68.51	72.00	88.52	84.00	**123.81**	5.05	442	1.04	0.15
1p	105.00	**112.29**	83.00	**101.34**	84.00	**105.65**	72.00	**103.18**	5.84	446	3.00	0.23
1q	90.00	93.78	80.00	97.05	68.00	82.80	63.00	87.70	5.84	446	2.66	0.23

* Relative inhibition (RI) of reference drug is taken as 100% for *E. coli*, *B. cereus*, *A. Candida*, and *R. Bataticola*.

*[2] Mutagenicity: compounds **1i** – high, **1o** – moderate, **1a–h,j–n,p,q** – no effect. Compounds **1a**–**q**: tumorigenicity – mild, no reproductive effect.

approved drugs and within the supposedly non-drug like collection of commercially available chemicals. A positive drug-likeness value (0.1–10) means that the molecule contains predominantly fragments which are frequently present in traded drugs. The OSIRIS calculations allow us to predict the toxicity risks in terms of mutagenicity, tumorigenicity, irritating, and reproductive effects. The Clog P is an important physicochemical property which indicates the lipophilicity and the ability of a molecule to cross biological membranes. According to Lipinski's rule of five, a Clog P value below 5 is feasible for a compound to be a future drug.

The synthesized compounds can be divided into three categories depending upon this evaluation: **1a–e** (no substituent on the phenyl group at the C(4) of the thiazole ring), **1f–k** (nitro group at the *para* position of the phenyl group on the C(4) of the thiazole ring), and **1l–q** (bromine atom at the *para* position of the phenyl group at the C(4) of the thiazole ring). Compounds **1a–k** show marginal lipophilicity within the range 4.0–5.0, and compounds **1l–q** have Clog P above 5. Compounds **1a–f** exhibit a drug score greater than 0.30, with **1l** scoring just below that value. With regard to their antibacterial properties, compounds **1a–e** and **1l** show good activity against both bacterial strains. Compounds **1a–d** and **1l** effectively inhibit the growth of both fungal strains. Hence, the drug score obtained by the OSIRIS Property Explorer can be at least tentatively correlated with the antimicrobial assay results. It is interesting to observe that compounds **1o** and **1p,** in spite of their lower drug score, have exhibited excellent activity against *R. bataticola* and **1p** against *A. candida*.

Drug toxicity is a factor of great importance for a potential commercial drug, since a significant number of drugs are disapproved in clinical trials based on their high toxicity profile. The toxicity of the compounds was calculated in terms of mutagenic, tumorigenic, reproductive, and irritant effect. Only compounds **1i** and **1o** exhibit mutagenic effect, and all the other compounds show very mild tumorigenic behavior, whereas none of the compounds show either reproductive effect or irritating effect. Hence, these compounds (except **1i** and **1o**) may be proposed as biologically safe for intake.

In summary, we have developed a simple, novel, and efficient protocol for the synthesis of a series of triazoles appended to thiazoles using catalytic amounts of $TiCl_4$ and studied their *in vitro* antibacterial and antifungal activity. The advantages of the present method are milder reaction conditions with better yields. The compounds were also tested for their toxicity, and their drug score was evaluated by property prediction software. The structure–activity relationship suggests that the compounds without any substituent on the phenyl ring attached to the thiazole are potent lead compounds for drug discovery with negligible toxicity.

EXPERIMENTAL

IR (KBr) spectra were recorded on a Nicolet-5700 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (300 and 75 MHz, respectinely) FT-NMR spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on a Shimadzu Japan QP2010 GCMS instrument. Elemental analyses were carried out using a Heraeus CHN Rapid Analyzer. Melting points were determined in open capillaries. Purity of the compounds was checked by TLC (ethyl acetate–hexane, 7:3).

Compounds **3a–f** were prepared according to the literature method [31].

3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-1,2,4-triazole-4-carbothioamide (**4a**). A mixture of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one **3a** (0.01 mol), $TiCl_4$ (10 mol %), and thiourea (0.01 mol) in absolute ethanol (10 ml) was refluxed for about 2 h. The reaction mixture was cooled and poured into ice. The obtained solid was filtered off and recrystallized from ethanol to give yellow needles, yield 87%; mp 146°C. IR spectrum, ν, cm^{-1}: 3444 (NH), 3327 (NH), 1707 (C=O), 1641 (C=N), 1424 (C=S). ^{1}H NMR spectrum, δ, ppm: 2.03 (2H, s, NH_2, D_2O exch.); 2.33 (3H, s, 5-CH_3); 7.24–7.79 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.0 (5-CH_3); 121.3; 121.6; 124.5; 129.0; 129.2; 137.7; 155.5; 157.5; 183.0. Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (13), 174 (10), 133 (100), 105 (20), 77 (65). Found, %: C 51.27; H 4.30; N 23.91. $C_{10}H_{10}N_4OS$. Calculated, %: C 51.20; H 4.37; N 23.85.

2-Aryl-4-(4-aryl-1,3-thiazol-2-yl)-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones 1a–q (General Method). A mixture of compound **3a–e** (0.001 mol), thiourea (0.001 mol), and $TiCl_4$ (10 mol%) in absolute ethanol (10 ml) and DMF (10 ml) was heated under reflux. After completion of the ring insertion of the nitrogen of thiourea (monitored by TLC), the corresponding bromoacetophenone **5–7** (0.001 mol) was added, and the mixture was stirred for 1.5–3 h at room temperature. The solid product was filtered and crystallized from ethanol to get pale-yellow needles of compounds **1a–q**.

5-Methyl-2-phenyl-4-(4-phenylthiazol-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1a), yield 87% (2.91 g); mp 130–131°C. IR spectrum, ν, cm^{-1}: 3018 (C–H), 1703 (C=O), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.50 (3H, s, 5-CH_3); 6.60 (1H, s, H-5'); 7.00–7.65 (10H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.5 (CH_3); 99.4; 121.0; 121.5; 124.0; 128.0; 128.2; 128.8; 129.0; 129.1; 129.5; 133.0; 134.5; 138; 148.5; 150.0; 152.0; 172.0. Mass spectrum, *m/z* (I_{rel}, %): 334 $[M]^+$ (14), 200 (100), 173 (12), 132 (34), 104 (50), 77 (62). Found, %: C 64.40; H 4.10; N 16.50. $C_{18}H_{14}N_4OS$. Calculated, %: C 64.65; H 4.22; N 16.75.

5-Methyl-4-(4-phenylthiazol-2-yl)-2-(*p*-tolyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1b), yield 92% (3.19 g); mp 175–176°C. IR spectrum, ν, cm^{-1}: 3026 (C–H), 1708 (C=O), 1644 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.30 (3H, s, CH_3 Ar); 2.55 (3H, s, 5-CH_3); 6.62 (1H, s, H-5'); 7.02–7.44 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.0 (CH_3); 23.5 (CH_3 Ar); 99.0; 120.0; 120.2; 125.0; 128.0; 128.2; 129.0; 130.2; 130.5; 131.0; 132.0; 133.1; 134.0; 137.4; 147.0; 149.0; 165.0. Mass spectrum, *m/z* (I_{rel}, %): 348 $[M]^+$ (8), 214 (24), 187 (100), 146 (16), 118 (43), 89 (65). Found, %: C 65.51; H 4.62; N 16.06. $C_{19}H_{16}N_4OS$. Calculated, %: C 65.50; H 4.63; N 16.08.

5-Methyl-4-(4-phenylthiazol-2-yl)-2-(*m*-tolyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1c), yield 92% (3.21 g); mp 112–113°C. IR spectrum, ν, cm^{-1}: 3039 (C–H), 1710 (C=O), 1642 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.35 (3H, s, CH_3 Ar); 2.45 (3H, s, 5-CH_3); 6.61 (1H, s, H-5'); 6.80–7.45 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.0; 24.0 (CH_3 Ar); 101.0; 118.5; 121.2; 121.4; 121.6; 124.5; 127.2; 127.4; 129.0; 129.3; 133.2; 137.0; 138.5; 145.0; 148.0; 162.0. Mass spectrum, *m/z* (I_{rel}, %): 348 $[M]^+$ (12), 218 (18), 177 (70), 159 (100), 151 (40). Found, %: C 65.35; H 4.45; N 16.02. $C_{19}H_{16}N_4OS$. Calculated, %: C 65.50; H 4.63; N 16.08.

2-(*p*-Chlorophenyl)-5-methyl-4-(4-phenylthiazol-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1d), yield 89% (3.28 g); mp 126–127°C. IR spectrum, ν, cm^{-1}: 3042 (C–H), 1707 (C=O), 1639 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, 5-CH_3); 6.58 (1H, s, H-5'); 7.19–7.30 (5H, m, H Ar); 7.50 (2H, d, *J* = 7.2, H Ar), 7.64 (2H, d, *J* = 7.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.0; 100.0; 127.4; 127.6; 129.1; 129.5; 129.9; 130.0; 130.2; 130.5; 131.0; 132.0; 135.5; 136.0; 148.5; 150.0; 154.8; 166.0. Mass spectrum, *m/z* (I_{rel}, %): 370 $[M+2]^+$ (17), 368 $[M]^+$ (48), 236 (11), 234 (29), 209 (08), 207 (20), 182 (100), 168 (7), 166 (18), 140 (9), 138 (20), 112 (10), 110 (31). Found, %: C 58.50; H 3.42; N 15.00. $C_{18}H_{13}ClN_4OS$. Calculated, %: C 58.61; H 3.55; N 15.19.

2-(*m*-Chlorophenyl)-5-methyl-4-(4-phenylthiazol-2-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1e), yield 90% (3.34 g); mp 165–166°C. IR spectrum, ν, cm^{-1}: 3048 (C–H), 1704 (C=O), 1637 (C=N). ^{1}H NMR spectrum, δ, ppm: 2.48 (3H, s, 5-CH_3); 6.59 (1H, s, H-5'); 7.04–7.65 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 25.8; 90.5; 119.5; 122.0; 124.5; 127.5; 128.0; 129.0; 129.5; 129.8; 130.4; 133.0; 134.5; 139.2; 148.2; 152.0; 155.0; 173.2. Mass spectrum, *m/z* (I_{rel}, %): 370 $[M+2]^+$ (9), 368 (25), 236 (22), 234 (20), 209 (29), 181 (100), 183 (19). Found, %: C 58.52; H 3.48; N 15.08. $C_{18}H_{13}ClN_4OS$. Calculated, %: C 58.61; H 3.55; N, 15.19.

5-Methyl-4-[4-(*p*-nitrophenyl)thiazol-2-yl]-2-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1f), yield 90% (3.42 g); mp 128–129°C. IR spectrum, ν, cm^{-1}: 3026 (C–H), 1708 (C=O), 1645 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (3H, s, 5-CH_3); 6.56 (1H, s, H-5'); 7.10–7.65 (5H, m, H Ar); 7.74 (2H, d, *J* = 8.4, H Ar); 8.25 (2H, d, *J* = 8.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.0; 89.4; 122.0; 122.5; 123.0; 123.5; 124.4; 128.5; 128.7; 129.0; 129.4; 137.6; 140.2; 148.0; 148.6; 152.0; 155.0; 170.5. Mass spectrum, *m/z* (I_{rel}, %): 379 $[M]^+$ (11), 200 (43), 173 (100), 132 (51), 104 (8), 77 (62). Found, %: C 56.88; H 3.43; N 18.39. $C_{18}H_{13}N_5O_3S$. Calculated, %: C 56.98; H 3.45; N 18.46.

5-Methyl-4-[4-(*p*-nitrophenyl)thiazol-2-yl]-2-(*p*-tolyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1g), yield 89% (3.53 g); mp 145–146°C. IR spectrum, ν, cm^{-1}: 3048 (C–H), 1702 (C=O), 1648 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.55 (3H, s, 5-CH_3); 2.35 (3H, s, CH_3 Ar); 6.58 (1H, s, H-5'); 7.05 (2H, d, *J* = 7.4, H Ar); 7.48 (2H, d, *J* = 7.4, H Ar); 7.78 (2H, d, *J* = 8.0, H Ar); 8.28 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.0 (CH_3); 25.0 (CH_3 Ar); 105.0; 121.6; 122.0; 130.5; 130.8; 134.0; 134.6; 135.0; 140.2; 148.0; 148.6; 128.4; 128.6; 149.0; 153.0; 155.0; 168.0. Mass spectrum, *m/z* (I_{rel}, %): 393 $[M]^+$ (16) 214 (36), 187 (62), 146 (43), 118 (100), 89 (62). Found, %: C 57.96; H 3.80; N 17.75. $C_{19}H_{15}N_5O_3S$. Calculated, %: C 58.01; H 3.84; N 17.80.

5-Methyl-4-[4-(*p*-nitrophenyl)thiazol-2-yl]-2-(*m*-tolyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1h), yield 86% (3.39 g); mp 152–153°C. IR spectrum, ν, cm^{-1}: 3052 (C–H), 1706 (C=O), 1642 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 2.48 (3H, s, 5-CH_3); 6.64 (1H, s, H-5'); 7.10–7.49 (4H, m, H Ar); 7.74 (2H, d, *J* = 7.0, H Ar); 8.30 (2H, d, *J* = 7.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.5 (CH_3); 23.4 (CH_3); 95.0; 115.0; 120.8; 122.0; 122.7; 124.5; 127.0; 128.5; 128.9; 137.5; 138.6; 139.2; 148.0; 149.0; 155.0; 157.0; 175.0. Mass spectrum, *m/z* (I_{rel}, %): 393 $[M]^+$ (22), 214 (30), 173 (40), 132 (46), 104 (74), 77 (100). Found, %: C 57.90; H 3.82; N 17.78. $C_{19}H_{15}N_5O_3S$. Calculated, %: C 58.01; H 3.84; N 17.80.

2-(*p*-Anisyl)-5-methyl-4-[4-(*p*-nitrophenyl)thiazol-2-yl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1i), yield 87% (3.58 g); mp 180–181°C. IR spectrum, ν, cm^{-1}: 3064 (C–H), 1713 (C=O), 1646 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, 5-CH_3); 3.60 (3H, s, OCH_3); 6.64 (1H, s, H-5'); 7.42 (2H, d, *J* = 6.9, H Ar); 7.50 (2H, d, *J* = 7.0, H Ar); 7.70 (2H, d, *J* = 8.4, H Ar); 8.21 (2H, d, *J* = 8.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.5 (CH_3); 42.0 (OCH_3); 99.0; 114.5; 114.8; 121.5; 121.7; 122.0; 122.2; 124.7; 130.8; 137.7; 139.2; 146.0; 148.4; 152.0; 155.0; 156.9; 173.0. Mass spectrum, *m/z* (I_{rel}, %): 409 $[M]^+$ (14), 230 (100), 203 (40), 162 (60), 134 (40), 106 (36). Found, %: C 55.70; H 3.65; N 17.10. $C_{19}H_{15}N_5O_4S$. Calculated, %: C 55.74; H 3.69; N 17.11.

2-(*p*-Chlorophenyl)-5-methyl-4-[4-(*p*-nitrophenyl)thiazol-2-yl]-2,4-dihydro-1,2,4-triazole (1j), yield 92% (3.81 g); mp 137–138°C. IR spectrum, ν, cm^{-1}: 3058 (C–H), 1711 (C=O), 1640 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.41 (3H, s, 5-CH_3); 6.53 (1H, s, H-5'); 7.20 (2H, d, *J* = 7.2, H Ar); 7.55 (2H, d, *J* = 7.4, H Ar); 7.67 (2H, d, *J* = 8.0, H Ar); 8.19 (2H, d, *J* = 8.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 25.8; 86.0; 119.8; 120.0; 123.0; 123.5; 129.0; 129.2; 130.0; 130.4; 131.3; 136.0; 139.4; 150.0; 151.0; 154.0; 156.0; 162.0. Mass spectrum, *m/z* (I_{rel}, %): 415 $[M+2]^+$ (10), 413 $[M]^+$ (33), 234 (18), 236 (5), 209 (15), 207 (46), 166 (100), 168 (6), 140 (9), 138 (23), 114 (15), 112 (54). Found, %: C 52.20; H 2.88; N 16.90. $C_{18}H_{12}ClN_5O_3S$. Calculated, %: C 52.24; H 2.92; N 16.92.

2-(*m*-Chlorophenyl)-5-methyl-4[4-(*p*-nitrophenyl)thiazol-2-yl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1k), yield 92% (3.84 g); mp 165–166°C. IR spectrum, ν, cm^{-1}: 3046 (C–H), 1709 (C=O), 1637 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.52 (3H, s, 5-CH_3); 6.57 (1H, s, H-5'); 7.11–7.69 (4H, m, H Ar); 7.75 (2H, d, *J* = 7.0, H Ar); 8.10 (2H, d, *J* = 7.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.6; 92.0; 119.7; 120.8; 121.0; 122.0; 122.2; 122.8; 124.5; 134.5; 139.0; 139.8; 139.6; 146.0; 148; 155; 159; 168. Mass spectrum, *m/z* (I_{rel}, %): 415 $[M+2]^+$ (16), 413 $[M]^+$ (50), 236 (9), 234 (30), 209 (100), 207 (34), 168 (12), 166 (40), 114 (17), 112 (50). Found, %: C 52.18; H 2.90; N 16.89. $C_{18}H_{12}ClN_5O_3S$. Calculated, %: C 52.24; H 2.92; N 16.92.

4-[4-(*p*-Bromophenyl)thiazol-2-yl]-5-methyl-2-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1l), yield 91% (3.75 g); mp 187–188°C. IR spectrum, ν, cm^{-1}: 3036 (C–H), 1703 (C=O), 1648 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, 5-CH_3); 6.50 (1H, s, H-5'); 7.37–7.80 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.5; 100.8; 120.6; 120.8; 124.5; 128.5; 128.8; 129.4; 129.7; 123.5; 132.0; 132.2; 132.5; 137.9; 148.5; 155.0; 159; 170.3. Mass spectrum, *m/z* (I_{rel}, %): 414 $[M+2]^+$ (24), 412 $[M]^+$ (21), 205 (100), 178 (40), 137 (60), 109 (46), 81 (54). Found, %: C 52.30; H 3.15; N 13.50. $C_{18}H_{13}BrN_4OS$. Calculated, %: C 52.31; H 3.17; N 13.56.

4-[4-(*p*-Bromophenyl)thiazol-2-yl]-5-methyl-2-(*p*-tolyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1m), yield 88% (3.78 g); mp 151–152°C. IR spectrum, ν, cm^{-1}: 3037 (C–H), 1707 (C=O), 1641 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3 Ar); 2.48 (3H, s, 5-CH_3); 6.57 (1H, s, H-5'); 7.27 (2H, d, *J* = 7.7, H Ar); 7.37 (2H, d, *J* = 8.2, H Ar); 7.49 (2H, d, *J* = 8.0, H Ar); 7.50 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum,

δ, ppm: 20.0 (CH_3); 27.00 (CH_3 Ar); 97.5; 121.5; 121.8; 124.0; 124.5; 129.0; 129.4; 130.0; 130.2; 131.9; 132.2; 132.4; 134.0; 134.5; 155.0; 157.0; 175.0. Mass spectrum, *m/z* (I_{rel}, %): 428 $[M+2]^+$ (31), 426 $[M]^+$ (29), 221 (90), 194 (100), 166 (42), 138 (65), 110 (14). Found, %: C 53.40; H 3.50; N 13.07. $C_{19}H_{15}BrN_4OS$. Calculated, %: C 53.40; H 3.54; N 13.11.

4-[4-(*p*-Bromophenyl)thiazol-2-yl]-5-methyl-2-(*m*-tolyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1n), yield 91% (3.89 g); mp 109–110°C. IR spectrum, ν, cm^{-1}: 3061 (C–H), 1706 (C=O), 1639 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3 Ar); 2.42 (3H, s, 5-CH_3); 6.62 (1H, s, H-5'); 6.84–7.35 (4H, m, H Ar); 7.60 (2H, d, *J* = 6.8, H Ar); 8.50 (2H, d, *J* = 6.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 22.2 (CH_3); 23.0 (CH_3 Ar); 98.0; 115.5; 121.3; 122.0; 124.5; 126.4; 129.8; 130.0; 132.6; 133.4; 133.6; 137.7; 138.4; 148.0; 150.0; 154.0; 169.0. Mass spectrum, *m/z* (I_{rel}, %): 428 $[M+2]^+$ (25), 426 $[M]^+$ (21), 236 (9), 221 (40), 205 (100), 194 (62), 166 (35), 138 (40). Found, %: C 53.35; H 3.48; N 13.00. $C_{19}H_{15}BrN_4OS$. Calculated, %: C 53.40; H 3.54; N 13.11.

2-(*p*-Anisyl)-4-[4-(*p*-bromophenyl)thiazol-2-yl]-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1o), yield 86% (3.84 g); mp 210–211°C. IR spectrum, ν, cm^{-1}: 3043 (C–H), 1701 (C=O), 1645 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.42 (3H, s, 5-CH_3); 3.70 (3H, s, OCH_3); 6.48 (1H, s, H-5'); 7.20 (2H, d, *J* = 6.5, H Ar); 7.32 (2H, d, *J* = 6.6, H Ar); 7.40 (2H, d, *J* = 8.0, H Ar); 7.53 (2H, d, *J* = 8.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.0 (CH_3); 45.0 (OCH_3); 80.0; 110.0; 110.4; 122.4; 122.7; 123.0; 125.0; 128.8; 129.0; 130.1; 131.3; 132.4; 134.6; 150.0; 151.0; 156.0; 163.0. Mass spectrum, *m/z* (I_{rel}, %): 444 $[M+2]^+$ (18), 442 $[M]^+$ (15), 237 (100), 210 (9), 169 (67), 141 (50), 113 (69). Found, %: C 51.20; H 3.38; N 12.60. $C_{19}H_{15}BrN_4O_2S$. Calculated, %: C 51.48; H 3.41; N 12.64.

4-[4-(*p*-Bromophenyl)thiazol-2-yl]-2-(*p*-chlorophenyl)-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1p), yield 89% (3.98 g); mp 159–160°C. IR spectrum, ν, cm^{-1}: 3077 (C–H), 1717 (C=O), 1641 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, 5-CH_3); 6.60 (1H, s, H-5'); 7.17 (2H, d, *J* = 7.4, H Ar); 7.46 (2H, d, *J* = 7.6, H Ar); 7.40 (2H, d, *J* = 8.0, H Ar); 7.50 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.0 (CH_3); 94.0; 121.0; 123.0; 123.5; 128.8; 129.0; 130.2; 130.5; 131.0; 132.6; 132.9; 135.9; 143.0; 150.0; 153.0; 154.0; 168.0. Mass spectrum, *m/z* (I_{rel}, %): 449 $[M+4]^+$ (16), 447 $[M+2]^+$ (7), 445 $[M]^+$ (13), 243 (100), 216 (42), 175 (11), 147 (40), 119 (65). Found, %: C 48.26; H 2.68; N 12.50. $C_{18}H_{12}BrClN_4OS$. Calculated, %: C 48.29; H 2.70; N 12.51.

4-[4-(*p*-Bromophenyl)thiazol-2-yl]-2-(m-chlorophenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (1q), yield 87% (3.92 g); mp 196–197°C. IR spectrum, ν, cm^{-1}: 3072 (C–H), 1718 (C=O), 1640 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, 5-CH_3); 6.64 (1H, s, H-5'); 7.13–7.68 (8H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 24.5 (CH_3); 101.0; 119.2; 120.0; 121.2; 121.4; 123.0; 123.5; 124.0; 128.4; 138.0; 138.9; 139.2; 143.4; 148.0; 151.0; 157.0; 174.0. Mass spectrum, *m/z* (I_{rel}, %): 449 $[M+4]^+$ (21), 447 $[M+2]^+$ (16), 445 (8), 243 (75), 216 (100), 175 (60), 147 (40). Found, %: C 48.20; H 2.65; N 12.47. $C_{18}H_{12}BrClN_4OS$. Calculated, %: C 48.29; H 2.70; N 12.51.

Antimicrobial Activity Assay [31]**.** Compounds **1a–q** were screened for their *in vitro* antibacterial activity against *E. coli* and *C. bacillus* and antifungal activity against *A. candida* and *R. bataticola*. The reference drugs used were Norfloxacin and Griseofulvin, respectively. The tests were carried out with the title compounds and the reference drugs under identical conditions by the cup-plate method with 20 μg of the substance in 0.1 ml of DMF. The relative percentage inhibition was calculated by the zone of inhibition in comparison with the reference drug as follows:

$$\text{Relative inhibition, \%} = 100 \times (X - Y)/(Z - Y),$$

where X – total area of inhibition in test plate, Y – total area of inhibition in solvent (DMF) plate, Z – total area of inhibition in reference plate.

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REFERENCES

1. R. R. Kamble, P. R. Latthe, and B. V. Badami, *Heteroatom Chem.*, **18**, 50 (2007).
2. M. V. George and C. S. Angadiyavar, *J. Org. Chem*., **36**, 1589 (1971).
3. R. R. Kamble and B. S. Sudha, *J. Heterocycl. Chem*., **43**, 345 (2006).
4. A. Varvaresou, A. Tsantili-Kakoulidou, T. Siatra-Papastasikoudi, and E. Tiligada, *Arzneim. Forsch*., **50**, 48 (2000).
5. M. Gokce, B. Cakir, K. Earl, and M. Sahin, *Arch. Pharm*., **334**, 279 (2001).
6. O. Pintilie, L. Profire, V. Sunel, M. Popa, and A. Pui, *Molecules*, **12***,* 103 (2007).
7. M. Foroumadi, M. Mirzaei, and A. Shafiee, *Pharmazie*, **56***,* 610 (2001).
8. M. G. Mamolo, V. Falagiani, D. Zampieri, L. Vio, and F. Banfi, *Farmaco*, **56**, 587 (2001).
9. K. Zamani, K. Faghihi, I. Tofighi, and M. R. Shariatzadeh, *Turk. J. Chem*., **28**, 95 (2004).
10. F. Clerici, D. Pocar, M. Guido, A. Loche, V. Perlini, and M. Brufani, *J. Med. Chem*., **44**, 931 (2001).
11. T. Önkol, B. Çakir, M. F. Şahin, E. Yildirim, and K. Erol. *Turk. J. Chem*., **28**, 461 (2004).
12. S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, W. Filipelli, G. Falcone, L. Giordano, and M. Vitelli, *Bioorg. Med. Chem*., **9**, 2149 (2001).
13. L. Labanauskas, V. Kalcas, E. Udrenaite, P. Gaidelis, A. Brukštus, and V. Daukšas, *Pharmazie*, **56**, 617 (2001).
14. S. Oniga, A. E. Parvu, B. Tiperciuc, M. Palage, and O. Oniga, *Farmacia*, **59**, 44 (2011).
15. S. G. Wadodkar, S. O. Jinturkar, and A. V. Kasture, *Indian Drugs*, **16**, 119 (1979).
16. A. Tsuruoka, Y. Kaku, H. Kakinuma, I. Tsukada, M. Yanagisawa, K. Nara, and T. Naito, *Chem. Pharm. Bull*., **46**, 623 (1998).
17. H. G. Roscoe, D. A. Blickans, and D. Kupfer, US Pat. 3752893 (1971); *Chem. Abstr*., **79**, 96966 (1973).
18. I. Kayagil and S. Demirayak, *Phosphorus*, *Sulfur*, *Silicon*, *Relat. Elem*., **184**, 2197 (2009).
19. W. Weuffen, T. Pyl, W. Gruebner, and W. D. Juelich, *Pharmazie*, **20**, 629 (1965).
20. C. F. H. Allen and A. Bell, *Org. Synth*., **24**, 12 (1944).
21. R. M. Herbst and J. A. Garrison, *J. Org. Chem*., **18**, 872 (1953).
22. G. D. Buckley and N. H. Ray, *J. Chem. Soc*., 1156 (1949).
23. C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.,* **77**, 621 (1955).
24. W. Otting and H. A. Staab, *Liebigs Ann. Chem.*, **622**, 23 (1959).
25. G. W. Sawdey, *J. Am. Chem. Soc*., **79**, 1955 (1957).
26. H. C. Brown, H. J. Gisler, Jr., and M. T. Cheng, *J. Org. Chem*., **31**, 781 (1966).
27. Y. T. Reddy, P. N. Reddy, B. S. Kumar, P. Rajput, N. Sreenivasulu, and B. Rajitha, *Phosphorus, Sulfur, Silicon, Relat. Elem.,* **182**, 161 (2007).
28. H. Valizadeh, H. Gholipur, R. Zarrebin, M. Amiri, and M. R. Sabzi, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, **183**, 1552 (2008).
29. D. Basavaiah and A. J. Rao, *Synth. Commun.*, **32**, 195 (2002).
30. L. Cai, C. Brouwer, K. Sinclair, J. Cuevas, and V. W. Pike, *Synthesis*, 133 (2006).
31. S. G. Mallur and B. V. Badami, *Farmaco*, **55**, 65 (2000).
32. C. A. Lipinski, *Drug Discovery Today: Technologies*, **1**, 337, (2004).
33. *OSIRIS Property Explorer,* http://www.organic-chemistry.org/prog/peo.
34. S. Emami, A. Kebriaeezadeh, N. Ahangar, and R. Khorasani, *Bioorg. Med. Chem. Lett.,* **21**, 655 (2011).
35. A. T. Sangamwar, U. D. Deshpande, S. S. Pekamwar, and S. M. Vadvalkar, *Ind. J. Biotechnol*., **6**, 389 (2007).