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Design, Synthesis, Characterization and Antibacterial Activity of Some Novel Furan Supported 1,2,4-Triazoles

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A methodical approach to synthesize several novel 2-phenyl-4-methylfuran [2,3-*e*][1,2,4]triazolo [1,5-*c*]pyrimidine derivatives (**5a-c**) as final compounds, *N*-(4-imino-4-methylfuro [2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) by involving 2-amino-3-cyano-4-methyl furan **(1)** and *N*-(3-cyano-4-methylfuran)formimidic ethyl ether **(2)** and *N*'-((Z-(3-cyano-4-methylfuran-2-ylimino)methyl)benzohydrazides (**3a-c**) as intermediates and their antibacterial activity was tested. The chemical structures of all the newly synthesized intermediates and title compounds have been characterized by ^{1}H NMR, IR, HRMS and elemental analysis. Compounds **4a-c** and **5a-c** showed antibacterial activity against different bacterial strains.

Keywords: Furan, 1,2,4-triazole, Antibacterial activity.

INTRODUCTION

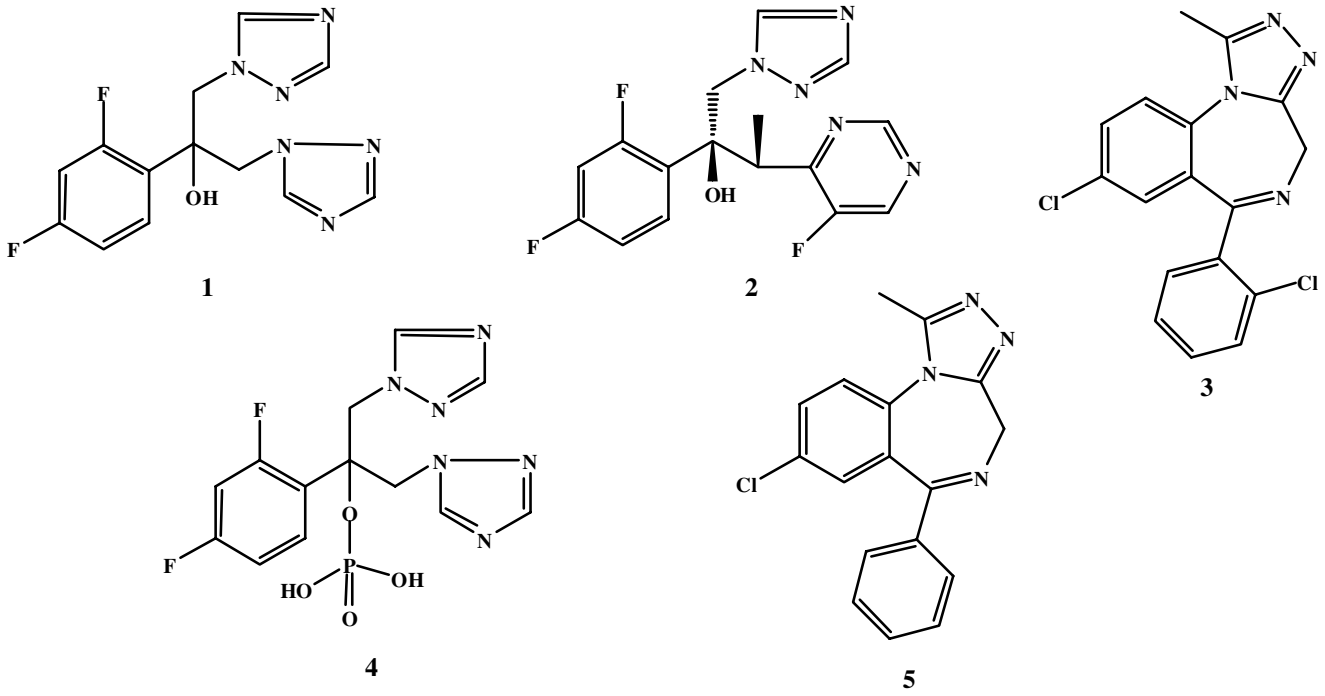
The chemistry of 1,2,4-triazole and their analogues has acquired substantial curiosity because of their important biological applications. For instance, a majority of 1,2,4-triazole systems were integrated within a broad diversity of medical fascinating drugs including anti-inflammatory [1], antianxiety [2], antimicrobial [3] and anticancer [4] namely, fluconazole, (**1**), voriconazole (**2**), *etc*. Additionally, some of well investigated drugs having 1,2,4-triazole moiety like triazolam (**3**), alprazolam (**4**) and fosfluconazole (**5**) [5] are also reported. In addition to that heterocycles with sulfur element constitute a prime group of compounds that are optimistic utilize in medical applications [6]. Majority of 1,2,4-triazoles were thoroughly examined and reported to exhibit wide range of biological applications like antibacterial [7], antitubercular [8] and antimycobacterial [9] activities.

On the other hand, various pyrimidine nuclei have been possess an extensive change of uses and its derivatives are also present in vitamin B_2 and folic acid. The pyrimidine skeleton considered as a privileged moiety in medicinal chemistry and biological fields. These are correlated with different therapeutic activities like anti-HIV [10], anti-tubercular [11], antitumor [12], anti-inflammatory [13], diuretic [14], antimalaria [15], cardiovascular [16]. Thus, the above mentioned facts motivate our interest to synthesize new compounds bearing furan supported 1,2,4-triazoles bearing pyrimidine ring.

EXPERIMENTAL

All the chemicals and solvents including solvents were obtained commercially from the reputed sources and used as such. Fisher-Johns melting point apparatus was used to identify the melting points and are uncorrected. All the prepared compounds were purified by column chromatography on silica gel (60–120 mesh). IR spectra have been attained on a Perkin-Elmer BX serried FTIR (5000) spectrometer utilizing KBr pellet. PMR spectra were documented on a Varian spectrometer (300 MHz). The position of the signals (chemical shift) was outlined in ppm while using tetramethyl silane as a standard. The mass fragmen-tation of all the synthesized compounds was measured with VG-Micromass 7070H spectrometer.

Synthesis of *N*-(3-cyano-4-methylfuran)formimidic ethyl ether (2): A solution of triethyl orthoformate (5 mL) and 2-amino-4-methylfuran-3-carbonitrile (**1**) (0.01 mol) was refluxed (5 h) with constant stirring. The solvent from the



Structure of some medicinal drugs containing 1,2,4-triazole systems

resulted solution was removed and the yielded crude was triturated with ethyl acetate to give a solid compound. It was accumulated by filtration and finally purified from ethyl acetate to offer *N*-(3-cyano-4-methylfuran)formimidic ethyl ether (**2**). Yield: 65%, pale yellow, m.p.: 114-116 ºC; IR (KBr, ν_{max}, cm^{-1}): 3025, 2958, 2236, 1616, 1597, 1024; PMR (δ, ppm, $CDCl_3$, 300 MHz): 5.85 (1H, s, NCH), 4.27 (1H, s, CH), 3.70 (2H, q, OCH_2, J = 5.8 Hz), 2.89 (3H, s, CH_3), 1.82 (3H, t, CH_3, J = 5.8 Hz). MS: 179 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_9H_{10}N_2O_2$: C, 60.66 (60.32); H, 5.66 (5.65); N, 15.72 (15.70); O, 17.96 (17.93).

Synthesis of *N′*-((Z-(3-cyano-4-methylfuran-2-ylimino)-methyl)benzohydrazides (3a-c): A suspension of *N*-(3-cyano-4-methylfuran)formimidic ethyl ether (**2**, 0.01 mol) and aryl hydrazide (0.01 mL) in ethanol (10 mL) was maintained at ambient temperature with constant stirring for 4-5 h. Then the mixture was poured into a cool water (15 mL) to acquire crude product after filtration and then purified with ethyl acohol to obtain *N′*-((Z-(3-cyano-4-methylfuran-2-ylimino)-methyl)-benzohydrazides (**3a-c**).

***N′*-((Z)-(3-Cyano-4-methylfuran-2-ylimino)methyl)-2-methoxybenzohydrazide (3a):** Yield: 72%, yellow, m.p.: 119-121 ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 3125, 3042, 2971, 2245, 1685, 1632, 1574, 1089; PMR (δ, ppm, $CDCl_3$, 300 MHz): 11.31 (1H, s, NH), 7.72 (1H, s, NH), 7.65-7.45 (4H, m, Ar), 5.87 (1H, s, =CH), 5.02 (1H, s, =CH), 2.72 (3H, s, CH_3), 2.10 (3H, s, 3H). MS: 299 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{15}H_{14}N_4O_3$: C, 60.40 (60.24); H, 4.73 (4.72); N, 18.78 (18.74); O, 16.09 (16.07).

***N′*-((Z)-(3-Cyano-4-ethylfuran-2-ylimino)methyl)-2-bromobenzohydrazide (3b):** Yield: 66%, yellow, m.p.: 109-111 ºC; IR (KBr, ν_{max}, cm^{-1}): 3328, 3238, 3040, 2960, 2242, 1675, 1660, 1575, 1078; PMR (δ, ppm, $CDCl_3$, 300 MHz): 11.37 (1H, s, NH), 7.69 (1H, s, NH), 7.64-7.41 (4H, m, Ar), 5.34 (1H, s, =CH), 5.08 (1H, s, =CH), 1.67 (3H, s, CH_3). MS: 347 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{14}H_{11}N_4O_2Br$: C, 48.43 (48.39); H, 3.19 (3.18); Br, 23.02 (23.00); N, 16.14 (16.12); O, 9.22 (9.21).

***N′*-((Z)-(3-Cyano-4-methylfuran-2-ylimino)methyl)-2-nitrobenzohydrazide (3c):** Yield: 65%, white, m.p.: 119-121 ºC; IR (KBr, ν_{max}, cm^{-1}): 3347, 3242, 3038, 2975, 2239, 1780, 1665, 1574, 1565, 1074; PMR (δ, ppm, $CDCl_3$, 300 MHz): 11.31 (1H, s, NH), 7.62 (1H, s, NH), 7.55-7.38 (4H, m, Ar), 5.29 (1H, s, =CH), 5.02 (1H, s, =CH), 1.71 (3H, s, CH_3). MS: 315 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{14}H_{12}N_5O_4$: C, 53.50 (53.45); H, 3.85 (3.84); N, 22.28 (22.25); O, 20.36 (20.33).

Synthesis of *N*-(4-imino-4-methylfuro[2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides (4a-c): A mixture consisting *N′*-((Z-(3-cyano-4-methylfuran-2-ylimino)methyl)benzohydrazides (**3a-c**) (0.01mol) in DMF (5 mL) was heated at reflux temperature for 3-4 h. The obtained solution was poured into cool water. Thus, obtained solid was filtered and purified with ethyl alcohol to obtain *N*-(4-imino-4-methylfuro[2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) in pure form.

***N*-(4-Imino-5-methylfuro[2,3-*d*]pyrimidine-3(4*H*)-yl)-2-methoxybenzamide (4a):** Yield: 71%, brown, m.p.: 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 3225, 3035, 2985, 1685, 1645, 1578, 1058; PMR (δ, ppm, $CDCl_3$, 300 MHz): 10.52 (1H, s, NH), 7.54 (1H, s, NH), 7.62-7.35 (4H, m, Ar), 5.41 (1H, s, =CH), 5.12 (1H, s, CH), 1.62 (3H, s, CH_3), 1.48 (3H, s, CH_3). MS: 299 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{15}H_{14}N_4O_3$: C, 60.40 (60.25); H, 4.73 (4.72); N, 18.78 (18.76); O, 16.09 (16.07).

***N*-(4-Imino-5-methylfuro[2,3-*d*]pyrimidine-3(4*H*)-yl)-2-bromobenzamide (4b):** Yield: 74%, yellow, m.p.: 142-144

ºC; IR (KBr, ν_{max}, cm^{-1}): 3258, 3048, 2935, 1680, 1655, 1574, 1065; PMR (δ, ppm, $CDCl_3$, 300 MHz): 10.35 (1H, s, NH), 7.75 (1H, s, NH), 7.72-7.35 (4H, m, Ar), 5.36 (1H, s, =CH), 5.20 (1H, s, =CH), 1.42 (3H, s, CH_3). MS: 347 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{14}H_{11}N_4O_2Br$: C, 48.43 (48.40); H, 3.19 (3.18); Br, 23.02 (23.00); N, 16.14 (16.12); O, 9.22 (9.21).

***N*-(4-Imino-5-methylfuro[2,3-*d*]pyrimidine-3(4*H*)-yl)-2-nitrobenzamide (4c):** Yield: 66%, brwon, m.p.: 114-116 ºC; IR (KBr, ν_{max}, cm^{-1}): 3245, 3028, 2965, 1668, 1655, 1578, 1568, 1074; PMR (δ, ppm, $CDCl_3$, 300 MHz): 10.25 (1H, s, NH), 7.45 (1H, s, NH), 7.52-7.37 (4H, m, Ar), 5.30 (1H, s, =CH), 5.17 (1H, s, =CH), 1.38 (3H, s, CH_3). MS: 315 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{14}H_{12}N_5O_4$: C, 53.50 (53.25); H, 3.85 (3.84); N, 22.28 (22.26); O, 20.36 (20.34).

Synthesis of 3-phenyl-4-methylfuran[2,3-*e*]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (5a-c): A mixture of *N*-(4-imino-4-methylfuro [2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) and chloroform (7 mL) was refluxed for 9-11 h. The product was collected on filtration and purified from ethanol to yield 2-phenyl-4-methylfuran [2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine (**5a-c**) in pure form.

3-(2-Methoxyphenyl)-4-methylfuran[2,3-*e*]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (5a): Yield: 70%, white, m.p.: 150-152 ºC; IR (KBr, ν_{max}, cm^{-1}): 3034, 2968, 1648, 1565, 1070; PMR (δ, ppm, $CDCl_3$, 300 MHz): 7.65-7.41 (4H, m, Ar), 5.28 (1H, s, =CH), 5.08 (1H, s, =CH), 1.55 (3H, s, CH_3), 1.38 (3H, s, CH_3). MS: 281 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{15}H_{12}N_4O_2$: C, 64.28 (64.23); H, 4.32 (4.31); N, 19.99 (19.97); O, 11.42 (11.40).

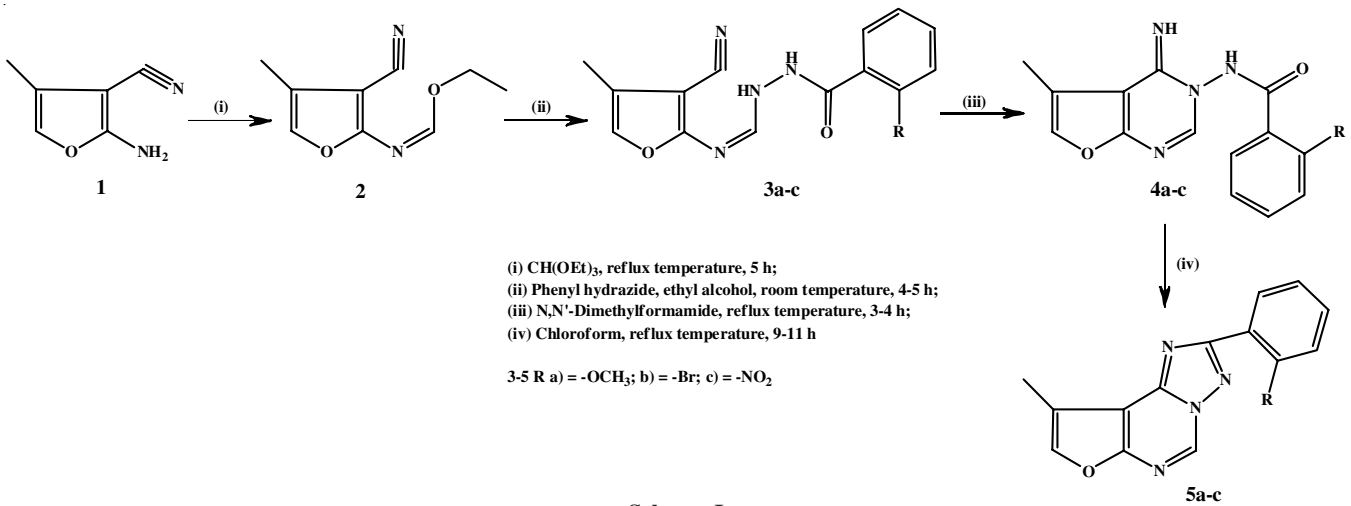
3-(2-Bromophenyl)-4-methylfuran[2,3-*e*]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (5b): Yield: 69%, yellow, m.p.: 125-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3040, 2974, 1650, 1570, 1064; PMR (δ, ppm, $CDCl_3$, 300 MHz): 7.58-7.36 (4H, m, Ar), 5.24 (1H, s, =CH), 5.02 (1H, s, =CH), 1.48 (3H, s, CH_3). MS: 329 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{14}H_9N_4OBr$: C, 51.09 (51.04); H, 2.76 (2.75); Br, 24.28 (24.25); N, 17.02 (17.00); O, 4.86 (4.85).

3-(2-Nitrophenyl)-4-methylfuran[2,3-*e*]-[1,2,4]triazolo[1,5-]pyrimidine (5c): Yield: 72%, white, m.p.: 132-134 ºC; IR (KBr, ν_{max}, cm^{-1}): 3058, 2965, 1648, 1584, 1512, 1086; PMR (δ, ppm, $CDCl_3$, 300 MHz): 7.70-7.29 (4H, m, Ar), 5.30 (1H, s, =CH), 5.14 (1H, s, =CH), 1.39 (3H, s, CH_3). MS: 297 (*m/z*, M^++1). Elemental analysis of calcd. (found) % $C_{14}H_{10}N_5O_3$: C, 56.76 (56.71); H, 3.40 (3.90); N, 23.64 (23.62); O, 16.20 (16.18).

RESULTS AND DISCUSSION

The target moieties have been synthesized by selecting 2-amino-4-methylfuran-3-carbonitrile (**1**) as starting compound and by involved *N*-(3-cyano-4-methylfuran)formimidic ethyl ether (**2**), *N'*-((Z-(3-cyano-4-methylfuran-2-ylimino)methyl)-benzohydrazides (**3a-c**) and *N*-(4-imino-4-methylfuro[2,3-*d*]-pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) as reactive intermediates. Thus, according to the synthetic method stipulated in **Scheme-I**, the preliminary intermediate **2** was obtained from the reaction executed from 2-amino-4-methyl-furan-3-carbonitrile (**1**) and triethyl orthoformate under reflux for 5 h on steady stirring. Compound **2** is authenticated by different spectroscopic techniques. The IR spectrum of this compound exhibited various stretching bands at 3025 (=C-H), 2958 (C-H, CH_3), 2236 (C≡N), 1616 (C=C), 1597 (C=N), 1024 (C-O) cm^{-1}. The resonance frequency of =CH group in its PMR spectrum at δ 5.85 ppm appeared as singlet. The single proton of another CH group is resonated as singlet at δ 4.85 ppm. The quartet signal at chemical shift 3.68 ppm and the triplet signal at 1.82 ppm with equal coupling constant (5.4 Hz) indicated the presence of ethyl (CH_3-CH_2) group. Finally, the CH_3 group is located as singlet at δ 2.89 ppm. The presence of molecular ion peak at *m/z* 179 in its mass spectrum correlated with the molecular weight.

Then the initial intermediate, *N*-(3-cyano-4-methylfuran)-formimidic ethyl ether (**2**) is changed into further intermediate, *N'*-((Z-(3-Cyano-4-methylfuran-2-ylimino)-methyl)-benzohydrazides (**3a-c**) on reaction with benzohydrazides in ethanol at ambient temperature on steady stirring for 4-5 h. The origin of intermediates **3a-c** is acquired by different spectral techniques. For instance, the absorption bands in the IR spectrum of **3a** disclosed at 3325 (N-H), 3125 (N-H), 3042 (C-H, Ar), 2971 (C-H, CH_3), 2245 (C≡N), 1685 (C=O), 1632 (C=C, Ar), 1574



Scheme-I

(C=N), 1089 (C-O) cm^{-1}. In its PMR spectrum, both NH groups as singlet are located at their corresponding chemical shifts such as 11.58 ppm and 7.62 ppm. All the four protons of phenyl group as multiplet located between δ 7.58-7.36 ppm. Similarly, both unsatuarted CH groups as singlet are emerged at δ 5.37 ppm and δ 5.02 ppm. Two singlet signals for each three protons at δ 1.79 ppm and δ 1.58 ppm are connected with methyl (CH_3) groups. In the mass spectrum, the molecular ion peak is observed at *m/z* 299 (M^+).

Subsequently, the final intermediate, *N*-(4-imino-4-methylfuro[2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) is attained on cyclization from *N*′-((Z-(3-cyano-4-methylfuran-2-ylimino)methyl)benzohydrazides (**3a-c**) in DMF at reflux temperature for 3-4 h. The evaluation of these compounds **4a-c** is acknowledged by mass, PMR and IR spectral inspection. The absorption bands in the IR spectrum of **4a** exhibited at 3225 (N-H), 3035 (C-H, Ar), 2985 (C-H, CH_3), 1685 (C=O), 1647 (C=C, Ar), 1578 (C=N), 1058 (C-O). In the PMR spectrum, the precessional frequencies at δ 10.52 ppm and δ 7.54 ppm for both protons of two NH groups appeared as singlets. The multiplet signal of four protons between δ 7.62-7.35 ppm is connected with phenyl group. Two singlet signals of both =CH groups are located at chemical shifts 5.41 ppm and 5.12 ppm. The signals observed at δ 1.62 ppm and δ 1.48 ppm as singlets are connected with both CH_3 groups. The molecular ion peak in its mass spectrum is observed at *m/z* 299 (M^+).

Eventually, compound *N*-(4-imino-4-methylfuro[2,3-*d*]-pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) in chloroform through cyclization at reflux temperature for 9-11 h is turned towards the target compounds, 2-phenyl-4-methylfuran[2,3-*e*]-[1,2,4]-triazolo[1,5-*c*]pyrimidine (**5a-c**) in notable yields. Emerging of compounds **5a-c** is authenticated by its different spectroscopic data. For illustration, compound **5a** disclosed the absorption bands in the IR spectrum at 3034 (C-H, Ar), 2968 (C-H, CH_3), 1648 (C=C, Ar), 1565 (C=N), 1070 (C-O) cm^{-1}. In the PMR spectrum, the signal located between δ 7.65-7.41 ppm for four protons as multiplet associated with phenyl ring. Two protons of both =CH groups as singlet are materialized at δ 5.28 and δ 5.08 ppm. Two singlet signals for each three protons of two CH_3 groups emerged with δ 1.55 ppm and 1.38 ppm. Finally, compound **5a** in its mass spectrum manifested the molecular ion peak at 281 (*m/z*, M^+).

Antibacterial activity: The contemporarily achieved products, *N*-(4-imino-4-methylfuro[2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides (**4a-c**) and 2-phenyl-4-methylfuran[2,3-*e*]-[1,2,4]-triazolo[1,5-*c*]pyrimidines (**5a-c**) were employed to estimate antibacterial activity (*in vitro*) towards some characteristic bacterial organs like *Salmonella typhimurium*, *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* by using broth dilution method [17] applying roxythromycin as reference compound and the assay has been discharged in duplicates. The mean diameters of inhibition zone (mm) have been documented. The consequences of this study of target compounds are shown in Table-1. Compound **5a** exhibited illustrious activity against *S. typhimurium*. The same compound **5a** accomplished notable activity towards *E. coli*. The rest of compounds expressed moderate to good activity. The outstanding activity of the title compounds justified future exploration in order to illuminate the way of action at molecular proportion.

TABLE-1
INHIBITION ZONE (mm) OF ANTIBACTERIAL SCREENING (*in vitro*) OF COMPOUNDS **4a-c** AND **5a-c**

Entry	*S. typhimurium*	*S. aureus*	*E. coli*	*B. subtilis*
4a	10	07	09	05
4b	12	11	12	14
4c	15	13	13	15
5a	22	22	22	13
5b	19	18	19	18
5c	14	15	18	16
Roxythromycin	28	25	27	26

Conclusion

A novel series of 2-phenyl-4-methylfuran[2,3-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidine derivatives has been achieved from *N*-(4-imino-4-methylfuro[2,3-*d*]pyrimidin-3(4*H*)-ylbenzamides by selecting 2-amino-3-cyano-4-methyl furan (**1**), which employed as a raw material in good to excellent yields. The title compounds were also used to evaluate for their antibacterial activity against different bacterial strains.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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