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Research Article

Synthesis, Antimicrobial Activity, Drug likeness and *In silico* Toxicity Study of Some Novel Triazole derivatives

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ABSTRACT

A series of novel 1,2,4- Triazole was synthesized and investigated for antimicrobial activity. The structures of all synthesized compounds were confirmed by means of elemental analysis, IR, ^{1}H NMR, and LCMS. All compounds were evaluated for antimicrobial activity cup plate method against *Staphylococcus aureus* (*S. aureus*), *Bacillus anthracis* (*B. anthracis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Candida albicans* (*C. albicans*) and *Aspergillus niger* (*A. niger*). Compounds 3a, 3b and 3e showed mild to moderate activity, whereas compounds 3c and 3d showed significant activity against gram-positive bacteria. In case of antifungal activity, compounds 3b and 3c showed mild to moderate activity against the fungal strains as compared with fluconazole. The predicted results showed that all of the compounds (3a-3f) may not have overall toxicity and any other kind of toxicity and showed great % absorbance ranging from 93.25 to 94.22%.

Introduction

It is estimated by the CDC (Centers for Disease Control) that 19 million new infections occur per year.[1-5] There are few serious problems that arise with the use of antimicrobial agents such as local irritancy, systemic toxicity, drug resistance, hypersensitivity, superinfection, nutritional deficiency and masking of an infection. [6-12] Bacteria and fungi generally develop drug resistance in three ways: producing metabolizing enzymes for the degradation of the drugs, modifying their targets to render the drugs ineffective, and expressing a high level of efflux proteins that 'pump' the drug out in order to lower its concentration. [13-17] The increasing cases of microbial resistance pose a major concern to the scientific community and have become a threat for human life worldwide.[18-19] Moreover, invasive microbial infections caused by multi-drug-resistant Gram-positive bacteria and microbes are difficult to diagnose and treat. They are the major cause of morbidity and mortality, especially in immunosuppressed and hospital-acquired patients.[20-22]

Day by day, new and stable antimicrobial agents with improved potency are needed to solve these problems.

Triazole moiety is a versatile lead molecule in pharmaceutical development and has a wide range of biological activities. Their derivatives are of great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities such as antiviral [23-24], antibacterial,[25-27] antifungal,[28-30] antituberculosis,[31-32] anticonvulsant [33-36], antidepressant [37-38], anti-inflammatory [39-40], anticancer [41-42] activities, etc.

In the present work, we planned to develop novel triazole derivatives and screen for antibacterial and antifungal activity.

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Material and Methods

The synthetic route used to synthesize title compounds is outlined in Fig. 1. MPs of the synthesized compounds were determined in open capillary tubes and are uncorrected. IR absorption spectra were recorded on Bruker alpha. Elemental analysis (C, H, and N) was undertaken with a Perkin-Elmer model 240C analyzer. ^{1}H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 MHz. The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer.

The compounds (1a-1f) were prepared by earlier reported literature.[43]

4-Phenyl-1-(2-(phenylamino)benzoyl) thiosemicarbazide (2a)

Equimolar amount of 2-(Phenylamino)benzohydrazide 1a and Phenyl isothiocyanate were refluxed for 4 h a mixture of 20 mL DMF and 40 mL ethanol. The reaction mixture was allowed to cool and then poured into ice cold water. The solid precipitated was filtered off and recrystallized.

MP: 206-208°C; Yield: 83 %; R_f value: 0.78; IR (υ_{max}, cm^{-1}): 3438, 3326 (NH), 2957, 2929 (Ar-CH), 1652 (C=O), 1436, 1415 (Ar. C=C), 1258 (C=S).

The similar procedure was adopted to synthesize remaining thiosemicarbazide derivatives (2b-2f) by using corresponding hydrazides (1b-1f).

1-(2-(*o*-Toluidino)benzoyl)-4-phenylthiosemicarbazide (2b)

MP: 210-212°C; Yield: 79 %; R_f value: 0.73; IR (υ_{max}, cm^{-1}): 3423, 3342 (NH), 2942, 2918 (Ar-CH), 1634 (C=O), 1452, 1429 (Ar. C=C), 1227 (C=S).

1-(2-(2,3-Dimethylphenylamino)benzoyl)-4-phenylthiosemicarbazide (2c)

MP: 222-224°C; Yield: 75 %; R_f value: 0.64; IR (υ_{max}, cm^{-1}): 3459, 3336 (NH), 2958, 2934 (Ar-CH), 1626 (C=O), 1447, 1412 (Ar. C=C), 1245 (C=S).

1-(2-Phenoxybenzoyl)-4-phenylthiosemicarbazide (2d)

MP: 216-218°C; Yield: 78 %; R_f value: 0.77; IR (υ_{max}, cm^{-1}): 3462, 3399 (NH), 2958, 2942 (Ar-CH), 1617 (C=O), 1329 (C–O-C), 1451, 1427 (Ar. C=C), 1207 (C=S).

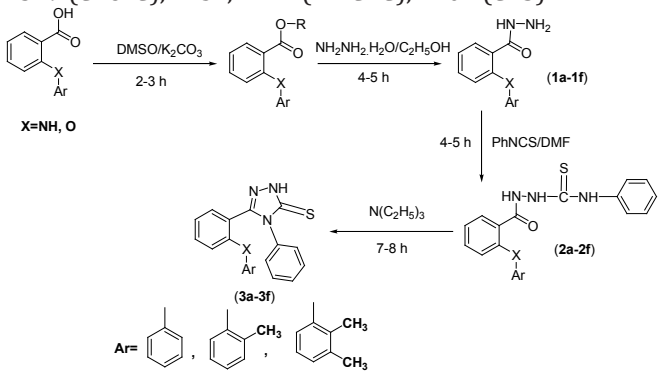

Fig. 1: Synthetic scheme of 1,2,4-triazoles (3a-3f)

4-Phenyl-1-(2-(*o*-tolyloxy)benzoyl) thiosemicarbazide (2e)

MP: 218-220°C; Yield: 72 %; R_f value: 0.72; IR (υ_{max}, cm^{-1}): 3418, 3387 (NH), 2948, 2916 (Ar-CH), 1631 (C=O), 1343 (C–O-C), 1452, 1437 (Ar. C=C), 1249 (C=S).

1-(2-(2,3-Dimethylphenoxy)benzoyl)-4-phenylthiosemicarbazide (2f)

MP: 222-224°C; Yield: 74 %; R_f value: 0.62; IR (υ_{max}, cm^{-1}): 3456, 3393 (NH), 2935, 2903 (Ar-CH), 1662 (C=O), 1357 (C–O-C), 1446, 1417 (Ar. C=C), 1228 (C=S).

4-Phenyl-5-(2-(phenylamino)phenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3a)

Ethanolic solution of 1 mmol of 4-Phenyl-1-(2-(phenylamino)benzoyl)thiosemicarbazide (**2a**) was refluxed with few drops of triethylamine as catalyst for 7-8 h. The solvent was evaporated and the precipitated product was recrystallized from appropriate solvents [44].

MP: 224-226°C; Yield: 84 %; R_f value: 0.88; Anal. Calcd. for $C_{20}H_{16}N_4S$ (344.43): C, 69.74; H, 4.68; N,16.27. Found: C, 68.06; H, 4.39; N, 16.54. IR (υ_{max}, cm^{-1}): 3446, 3314 (NH), 2962, 2938 (Ar-CH), 1572 (C=N), 1446, 1423 (Ar. C=C), 1236 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 4.28 (s, 1H, NH), 6.71-7.62 (m, 14H, Ar-H), 11.09 (s, 1H, NH). LCMS (m/z): $[M]^+$; 344.11.

Similarly triazole derivatives (3b-3f) were synthesized by using corresponding thiosemicarbazide derivative (2b-2f).

5-(2-(*o*-Toluidino)phenyl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione (3b)

MP: 228-230°C; Yield: 76 %; R_f value: 0.79; Anal. Calcd. for $C_{21}H_{18}N_4S$ (358.46): C, 70.36; H, 5.06; N,15.63. Found: C, 69.97; H, 5.34; N,15.32. IR (υ_{max}, cm^{-1}): 3456, 3339 (NH), 2957, 2927 (Ar-CH), 1586 (C=N), 1436, 1411 (Ar. C=C), 1255 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.19 (s, 3H, CH_3), 2.37 (s, 1H, NH), 6.54-7.89 (m, 13H, Ar-H), 11.23 (s, 1H, NH). LCMS (m/z): $[M+H]^+$; 359.13.

5-(2-(2,3-Dimethylphenylamino)phenyl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione (3c)

MP: 232-234°C; Yield: 72 %; R_f value: 0.69; Anal. Calcd. for $C_{22}H_{20}N_4S$ (372.49): C, 70.94; H, 5.41; N,15.04; Found: C, 71.27; H, 5.73; N,15.29. IR (υ_{max}, cm^{-1}): 3443, 3324 (NH), 2948, 2907 (Ar-CH), 1561 (C=N), 1457, 1426 (Ar. C=C), 1242 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.19 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.12 (s, 1H, NH). 6.73-7.51 (m, 12H, Ar-H), 11.34 (s, 1H, NH). LCMS (m/z): $[M]^+$; 372.14.

5-(2-Phenoxyphenyl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione (3d)

MP: 220-224°C; Yield: 81 %; R_f value: 0.86; Solvent system: Benzene: Ethylacetate (8:2). Anal. Calcd. for $C_{20}H_{15}N_3OS$ (345.42): C, 69.54; H, 4.38; N,12.17. Found: C, 69.37; H, 4.64; N,11.89. IR (υ_{max}, cm^{-1}): 3454, 3387 (NH), 2979, 2943 (Ar-CH), 1582 (C=N), 1352 (C–O-C), 1472, 1443 (Ar. C=C),

1236 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 10.89 (s, 1H, NH), 6.88-7.62 (m, 14H, Ar-H). LCMS (m/z): $[M]^+$; 345.09.

4-Phenyl-5-(2-(*o*-tolyloxy)phenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3e)

MP: 216-218°C; Yield: 77 %; R_f value: 0.84; Anal. Calcd. for $C_{21}H_{17}N_3OS$ (359.44): C, 70.17; H, 4.77; N,11.69. Found: C, 79.86; H, 4.34; N,11.98. IR (υ_{max}, cm^{-1}): 3427, 3374 (NH), 2982, 2939 (Ar-CH), 1574 (C=N), 1337 (C–O-C), 1468, 1426 (Ar-C=C), 1255 (-C=S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.29 (s, 3H, CH_3), 11.21 (s, 1H, NH), 6.51-7.81 (m, 13H, Ar-H). LCMS (m/z): $[M]^+$; 359.11.

5-(2-(2,3-Dimethylphenoxy)phenyl)-4-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione (3f)

MP: 232-234°C; Yield: 83 %; R_f value: 0.87; Anal. Calcd. for $C_{22}H_{19}N_3OS$ (373.47): C, 70.75; H, 5.13; N,11.25. Found: C, 70.47; H, 5.28; N,11.01. IR (υ_{max}, cm^{-1}): 3446, 3369 (NH), 2964, 2927 (Ar-CH), 1565 (C=N), 1363 (C–O-C), 1456, 1433 (Ar-C=C), 1241 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.17 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.91-7.48 (m, 12H, Ar-H), 11.07 (s, 1H, NH). LCMS (m/z): $[M+H]^+$; 374.13.

In vitro Antimicrobial Activity

The synthesized compounds (3a-3f) were screened for antimicrobial activity, and cup plate method was used for the determination zone of inhibition.

Two gram-positive bacterial strains *Staphylococcus aureus, Bacillus anthracis,* two gram-negative bacterial strains *Pseudomonas aeruginosa and Escherichia coli* were used for the determination of antibacterial activity. Two fungal strains *C. albicans* and *A. niger* were used for the determination of antifungal activity. Streptomycin and fluconazole were used as standard for antibacterial and antifungal activity, respectively. DMSO was used as solvent control. Nutrient broth and Sabourd dextrose broth were used as Culture Media for bacteria and fungi, respectively. [45] Sterile nutrient broth/sabourd dextrose broth plates were prepared by pouring the sterile agar into petri dishes in aseptic conditions. 0.1 mL of each standardized test organism were spreaded into agar plates. Holes were prepared by using a sterile borer of diameter 6 mm. The test drug as well as the standard drug and the solvent control were placed in each hole separately. Then the plates were maintained at 4°C for 1 h to allow the diffusion of solution into the medium. All the bacterial plates were incubated at 37°C for 24 h and fungal plates at 25°C for 48hours. The zone of inhibition was measured in mm.[45]

Table 1: Antibacterial activity of title compounds

Comp (1000 µg/mL)	*Zone of inhibition (mm)*			
	S. aureus	*B. anthracis*	*P. aeruginosa*	*E. coli*
Streptomycin	33	34	28	29
3a	16	12	11	13
3b	17	12	20	14
3c	25	21	19	23
3d	21	18	17	20
3e	15	17	19	14
3f	10	15	14	11

In-silico Prediction of Toxicity

The possible toxicity of the synthesized compounds was predicted by using Pallas version 3.1 tool. The application was initialized by double-click on the tool icon. In New menu (appeared at the main window of Pallas), the molecule to be analyzed was drawn by the worksheet of Pallas; then, with the help of select menu, molecule was subjected for prediction (option) of toxicity by Hazardexpert/ ToxAlert and noted.[46-48]

In-silico Prediction of Absorption and Drug Likeness

The calculation of molecular properties like drug likeliness and bioactivity were predicted by the molinspiration property engine v2009.01 program.

The Molinspiration home page was opened online, in which free online cheminformatics services link option was opened. The molecule to be analyzed was pasted, whose structure was already saved in smile format (through any chemistry software) then with the help of calculate properties or predict bioactivity options, calculations were obtained and saved.[48-49]

"Lipinski rule or rule of five is like that to be drug-like, a candidate should have less than five hydrogen bond donors (HBD), less than 10 hydrogen bond acceptors (HBA), a molecular weight of less than 500 Da, and a partition coefficient log P of less than 5. The aim of the *rule of five* is to highlight possible bioavailability problems if two or more properties are violated".[50]

"Absorption (%ABS) was calculated by %ABS = 109-(0.345 X TPSA)". [50]

Results and Discussion

The title compounds (**3a-3f**) were synthesized as per the scheme. In the first step, hydrazide derivatives (**1a-1f**) were synthesized from aromatic acids in two steps *i.e.*

Table 2: Antifungal activity of title compounds

Compound (1000 µg/mL)	*Zone of Inhibition (mm)*	
	C. albicans	*A. niger*
Fluconazole	28	26
3a	11	07
3b	21	18
3c	17	19
3d	14	13
3e	16	13
3f	09	12

Table 3: *In-silico* toxicity study of title compounds

Compound Name	*Toxicity*	*Overall Toxicity*	*Oncogenicity*	*Mutagenicity*	*Teratogenicity*	*Irritation*	*Sensitivity*	*Immunotoxicity*	*Neurotoxicity*
3a	Not probable	0	0	0	0	0	0	0	0
3b	Not probable	0	0	0	0	0	0	0	0
3c	Not probable	0	0	0	0	0	0	0	0
3d	Not probable	0	0	0	0	0	0	0	0
3e	Not probable	0	0	0	0	0	0	0	0
3f	Not probable	0	0	0	0	0	0	0	0

Table 4: Drug likeliness and *in-silico* prediction of % absorption

Compounds	*Log P*	*MW*	*nrotb*	*nON*	*MV*	*nOHNH*	*nviolation*	*TPSA*	*% abs*
3a	4.78	344.44	4	4	304.73	2	0	45.64	93.25
3b	5.08	358.47	4	4	321.29	2	1	45.64	93.25
3c	5.58	372.50	4	4	337.85	2	1	45.64	93.25
3d	4.54	345.43	4	4	301.31	1	0	42.85	94.22
3e	4.94	359.45	4	4	317.87	1	0	42.85	94.22
3f	5.34	373.48	4	4	334.43	1	1	42.85	94.22

MW: molecular weight, **nrotb:** no. of rotatable bonds, **nON:** number of hydrogen bond acceptors, **MV:** molecular volume, **nOHNH:** number of hydrogen bond donors, **nviolation:** number of violations **% TPSA:** Total Polar Surface Area, **abs:** percentage of absorption

esterification followed by reacting with hydrazine hydrate. IR spectra confirmed the structures with appearance of NH_2 peak. In the second step, thiosemicarbazide derivatives (**2a-2f**) were synthesized from hydrazides (**1a-1f**) with phenyl isothiocynate. IR spectra confirmed the structures with appearance of C=S peak. In the final step, Triazoles (**3a-3f**) derivatives were synthesized by cyclization of thiosemicarbazide derivatives (**2a-2f**) by using triethylamine. The structures of title compounds (**3a-3f**) were confirmed by IR spectra with the disappearance of C=O peak and also confirmed by ^{1}H NMR and LCMS. The purity of compounds was also ascertained by Elemental analysis (C, H and N).

In vitro Antimicrobial Activity

All the title compounds synthesized (Compounds **3a-3f**) were tested against two gram-positive bacterial strains *Staphylococcus aureus, Bacillus anthracis,* two gram-negative bacterial strains *Pseudomonas aeruginosa, Escherichia coli* and two fungal strain (*C. albicans, A. niger*) by cup-plate method for antimicrobial activity. For the study, the solutions of 1000 µg/mL concentration of test compounds were prepared in dimethylsulphoxide (solvent). Streptomycin and fluconazole were used as standard for antibacterial and antifungal activity, respectively. Both standard drug control and solvent control were maintained for the study.[45]

In case of antibacterial activity, the zone of inhibition was ranging from 10 to 25 mm and 11 to 23 mm for gram-positive bacterial and gram negative bacterial strains, respectively.

At the same time, it was noted that compounds 3a, 3b and 3e showed mild to moderate activity, whereas compounds 3c and 3d showed significant activity against gram-positive bacteria.

In case of antifungal activity, the zone of inhibition ranged from 07 to 21 mm and the compounds 3b and 3c showed mild to moderate activity against the fungal strains compared with fluconazole (Tables 1 and 2).

In-silico Prediction of Toxicity/Metabolites

The toxicity of a molecule is highly dependent upon its structural elements. The *in-silico* toxicity study was performed by using pallas 3.1 (Toxalert) software to predict overall toxicity, oncogenicity, mutagenicity, teratogenicity, irritation, sensitivity, immunotoxicity, and neurotoxicity."[46-48] The predicted results showed that all of the compounds (3a-3f) might not have overall toxicity, oncogenicity, mutagenicity, teratogenicity, irritation, sensitivity, immunotoxicity, and neurotoxicity Table 3.

In-silico Prediction of Absorption and Drug Likeness

The calculation of molecular properties like drug likeliness and bioactivity were predicted by the Molinspiration property engine v2009.01 program. It was observed that all the compounds (3a-3f) exhibited a great% Absorbance ranging from 93.25 to 94.22% (Table 4).

Conclusion

1,2,4-Triazoles and their condensed derivatives constitute an important class of heterocycles with various pharmacological activities. All the title compounds synthesized (3a-3f) were tested against 2 gram +ve bacterial strains *S. aureus, B. anthracis,* 2 gram -ve bacterial strains *P. aeruginosa, E. coli,* and 2 fungal strains (*A. niger,*

C. albicans,) by cup-plate method for antimicrobial activity. Compounds 3a, 3b and 3e showed mild to moderate activity, whereas compounds 3c and 3d showed significant activity against gram-positive bacteria, and compounds 3b and 3c showed mild to moderate activity against the fungal strains as compared with fluconazole. The predicted results showed that all of the compounds (3a-3f) may not have any kind of toxicity. It was observed that all the compounds (3a-3f) exhibited a great % Absorbance ranging from 93.25 to 94.22%.

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