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Synthesis, Characterization, PASS Prediction and *in silico* ADME Studies of Ester and Ether Linked 1,4-Disubstituted 1,2,3-Triazoles Derivatives *via* Click Approach

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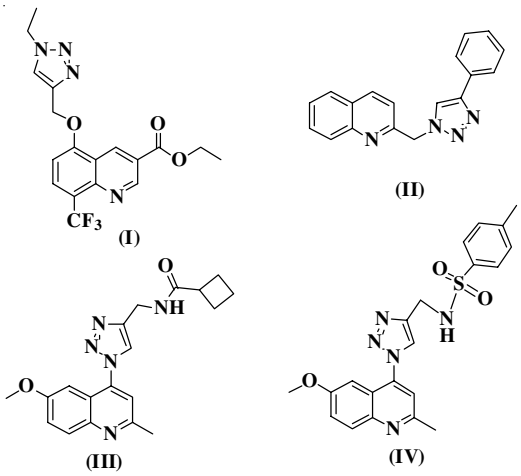
In the present investigation, we focused our interest on the synthesis of pharmacophoric units (quinoline and 1,2,3-triazole) linked through ester (**3a-b**) and (substituted aromatic ring and 1,2,3-triazole) linked through an ether (**3c-h**). The synthesis involves multiple sequence of reactions *viz*. diazotization reaction followed by nucleophilic substitution and finally Cu(I)-catalyzed alkyne azide cycloaddition reaction (CuAAC). The assigned structures of the compound were confirmed by ^{1}H & ^{13}C NMR and mass spectrometry. Prediction of activity spectra for substances (PASS) training set for the synthesized compounds were carried out using PASS software. Interestingly, PASS prediction of the compounds (**3a-h**) showed that the compounds are more potent as anti-inflammatory (Pa < 0.65) compared to antibacterial (Pa < 0.33) as well as antifungal agents (Pa < 0.35). Furthermore, these compounds were subjected to *in silico* ADMETox evaluation. All the compounds were found to pass the ADME evaluation and only few compounds passed the predicted toxicity evaluation. This work could be used as an initial approach in identifying potential novel molecules with promising activity and low toxicity.

Keywords: 1,2,3-Triazole, 1,3-Dipolar cycloaddition, Aromatic Azides, Prediction of activity spectra for substances, Druglikeness.

INTRODUCTION

Heterocyclic moieties are the most important pharmacologically active structural units and attracted a lot of attention among the medicinal chemist and biologist who are involved in the process of developing new drug candidates [1]. Among the heterocyclic moieties quinoline and its derivatives form a class of such a molecular moiety because of their wide variety of pharmacological activities such as antimalarial (quinine, chloroquine), chemotherapeutic activity (topotecan), antitubercular activity (mefloquine, moxifloxacin) *etc*. On the other hand azoles are most promising five membered nitrogen containing aromatic hetereocycles. Recent literature report identified that among the azoles (imidazole, pyrazole, triazole, tetrazole and pentazole), triazole containing three nitrogen compounds were the most recently studied in particular 1,2,3-traizoles [2-7]. These heterocycles have been well exploited for many medicinal scaffolds exhibiting anti-HIV, anticancer, anti-infective and antimicrobial activities [8-17]. These moieties also serves as key synthetic intermediates in many industrial applications such as agrochemicals [18-20], corrosion inhibitors [21,22], additives [23,24], supramolecular chemistry [25,26], dendrimers, polymers [27,28], liquid crystals [29,30], photostabilizers [31,32], pigments [33,34] and metal chelators [35,36]. Recent reports demonstrated that 1,2,3-traizole incorporated quinoline derivatives have wide variety of pharmacological applications like 8-trifluoromethyl quinoline based 1*H*-1,2,3-triazole derivatives (**I**) are found to be moderate antimicrobial agents [37]. A series of 2-quinoline-1*H*-1,2,3-triazole hybrids (**II**) exhibited inhibition activity against *M. tuberculosis* H37Rv strain [38]. The 6-methoxy-2-methylquinoline-1*H*-1,2,3-triazole core having amides (**III**) or sulphonamides (**IV**) exhibited promising antitubercular activity [39].

Considering the individual biological and medicinal importance of quinoline and 1,2,3-triazoles, we wanted to explore novel chemical entities based on quinoline and triazole moieties towards their biological significance. Hence, in the present study we focused our interest on the synthesis, charac-



terization and *in silico* assessment of drugability of 1,2,3-triazole derivatives (**3a-h**). One group of compounds was quinoline and 1,2,3-triazoles linked through ester linkage and another one substituted aromatic ring and 1,2,3-triazoles linked *via* ether linkage. Additionally, computational evaluation of antimicrobial and anti-inflammatory activities and ADMETox evaluation were carried out.

EXPERIMENTAL

The organic solvents and chemicals were purchased from SD Fine, Spectrochem, Sigma Aldrich and standard commercial sources are used without further purification. Melting point ranges of solid compounds were determined in open capillary tubes using a hot stage apparatus. Progress of the reactions was monitored by TLC using Merck silica gel 60 F_{254} precoated on aluminium backed plates. FTIR spectra were recorded using Shimadzu ATR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Agilent (400 MHz, ^{1}H NMR) and (100 MHz, ^{13}C NMR) spectrometers using deuteriated solvents ($CDCl_3$ or DMSO-d_6) and Tetramethylsilane (TMS) as an internal standard. The Mass spectra were recorded using Waters Alliance 2795 separation module and the Waters Micromass LCT mass detector.

General procedure for the synthesis of *o*-propargylated derivatives (1a-d): 4-Chloro phenol (or) 5-substituted salicyaldehyde (or) 2-phenyl quinoline-4-carboxylic acid (0.1 g, 0.001 mol) and K_2CO_3 (0.13 g, 0.001 mol) were taken in a round bottom flask containing DMF (5 mL). To this propargyl bromide (0.089 mL, 0.001 mol) was added drop-wise and resulting mixture was stirred at lab temperature for 12-18 h. The completion of conversion was monitored by disappearance of starting material in TLC. After completion of reaction, dilute the reaction mixture with 10 mL of ethyl acetate. The organic layer was washed with water followed by brine solution and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to get product of propynyloxy benzene and benzaldehyde derivatives (**1a-d**).

General procedure for the preparation of substituted azido benzene derivatives (2a-b): Substituted anilines (0.5 g, 0.0036 mol) were added to 10 mL of 2.4 N HCl taken in 100 mL round bottom flask and cooled to below 10 °C in an ice bath. After 30 min, $NaNO_2$ (0.496 g, 0.0072 mol) dissolved in 5 mL of water was added drop wise and stir it for 30 min. Then NaN_3 (0.468 g, 0.0072 mol) dissolved in 5 mL of water was carefully added dropwise to the above solution. After complete addition, the resulting mixture was stirred at room temperature for 1 h. The completion of conversion was monitored by disappearance of starting material in TLC. After completion of reaction, dilute the reaction mixture with 10 mL of diethyl ether. The organic layer was washed with water followed by brine solution and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to get solid azide derivatives (**2a-b**).

General procedure for the preparation of (ester and ether linked 1,4-disubstituted 1,2,3-triazoles (3a-h): Compound (**1a-d**) (0.2 g, 0.0012 mol), aryl azides (**2a-b**) (0.2 g, 0.0012 mol) were added to mixture of 3:1 (THF:H_2O) solvent taken in 100 mL round bottom flask and kept for stirring at room temperature. Then add $CuSO_4 \cdot 5H_2O$ (10 mol %) and sodium ascorbate (20 mol %) allow the resulting reaction mixture to stir at lab temperature for 24 h. The progress of the reaction was monitored using TLC. After completion of reaction, dilute the reaction mixture with 10 mL of ethyl acetate. The organic layer washed with water, brine and dried over anhydrous Na_2SO_4. The organic layer was evaporated under vacuum to residue further triturating with chloroform and hexane resulted in the desired solid products1,2,3-triazoles **(3a-h)**.

Spectral data

Prop-2-ynyl-2-phenylquinoline-4-carboxylate (1a): Yield: 90%, m.p.: 90-92 °C m.f. (m.w.): $C_{19}H_{13}NO_2$ (287.31); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 8.53-8.51 (d, 1H, J = 8.0 Hz, Ar-H), 8.42 (s, 1H, Ar-H), 8.25-8.23 (d, 2H, J = 8.0 Hz, Ar-H), 8.16-8.14 (d, 1H, J = 6.0 Hz, Ar-H), 7.86-7.82 (t, 1H, Ar-H), 7.72-7.68 (t, 1H, Ar-H), 7.57-7.51 (m, 3H, Ar-H), 5.136-5.130 (d, 2H, J = 2.4 Hz, -O-CH_2), 3.71 (s, 1H, ≡*C*-H). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 165.65, 156.32, 148.92, 138.24, 136.06, 131.02, 130.65, 130.51, 129.56, 128.73, 127.78, 125.46, 123.59, 119.99, 79.15, 78.59, 54.06; Mass: *m/z*: 288.01.

1-Chloro-4-(prop-2-ynyloxy) benzene (1b): Yield: 90%, m.p.: NA (oil). m.f. (m.w.): C_9H_7ClO (166.6); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 7.34-7.31 (d, 2H, J = 8.0 Hz, Ar-H), 7.00-6.97 (d, 2H, J = 8.0 Hz, Ar-H), 4.78-4.77 (d, 2H, J = 3.0 Hz, -O-CH_2), 3.55-3.54 (t, 1H, ≡*C*-H). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 162.89, 156.62, 129.80, 125.60, 117.25, 79.48, 78.95, 56.33.

5-Bromo-2-(prop-2-ynyloxy) benzaldehyde (1c): Yield: 90%, m.p.: 93-95 °C (lit. [40] 89-91 °C). m.f. (m.w.): $C_{10}H_7O_2Br$ (239.07); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 10.25 (s, 1H, CHO), 7.88-7.85 (dd, 1H, J = 8.0 & 5.0 Hz, Ar-H), 7.77-7.76 (d, 1H, J = 6.0 Hz, Ar-H), 7.30-7.28 (d, 2H, J = 5.0 Hz, Ar-H), 5.02-5.01 (d, 2H, J = 3.0 Hz, -O-CH_2), 3.71-3.70 (t, 1H, ≡*C*-H).

5-Nitro-2-(prop-2-ynyloxy) benzaldehyde (1d): Yield: 90%, m.p.: 90-92 °C (lit. [40] 89-91 °C). m.f. (m.w.): $C_{10}H_7NO_4$ (205.17); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 10.29 (s, 1H, CHO), 8.53-8.50 (dd, 1H, J = 8.0 & 5.0 Hz, Ar-H), 8.42-

8.41 (d, 1H, *J* = 6.0 Hz, Ar-H), 7.51-7.49 (d, 2H, *J* = 5.0 Hz, Ar-H), 5.16-5.15 (d, 2H, -O-CH_2), 3.75-3.74 (t, 1H, ≡*C*-H). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 188.12, 163.76, 141.82, 131.08, 124.90, 124.12, 115.68, 80.42, 78.10, 57.92.

(1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methyl-2-phenylquinoline-4-carboxylate (3a): Yield: 60%, m.p.: 172-178 °C. m.f. (m.w.): $C_{25}H_{17}N_5O_4$ (451.43); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 9.21 (s, 1H, triazole-H), 8.58-8.56 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.46 (s, 1H, Ar-H), 8.42-8.40 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.24-8.14 (m, 6H, Ar-H), 7.86-7.82 (t, 1H, Ar-H), 7.71-7.68 (t, 1H, Ar-H), 7.56-7.50 (m, 3H, Ar-H), 5.70 (s, 2H, CH_2); ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 166.06, 156.33, 148.92, 147.34, 143.95, 141.28, 138.27, 136.36, 130.99, 130.62, 132.46, 129.54, 128.67, 127.78, 126.06, 125.62, 124.28, 123.67, 121.27, 120.59, 59.16; Mass: *m/z*: 452.04.

(1-(4-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl) methyl-2-phenylquinoline-4-carboxylate (3b): Yield: 70%, m.p.: 201-204 °C. m.f. (m.w.): $C_{27}H_{20}N_4O_3$ (448.47); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 9.06 (s, 1H, triazole-H), 8.15-8.13 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.07-8.05 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.34-7.32 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.10-7.07 (d, 2H, *J* = 10.0 Hz, Ar-H), 5.24 (s, 2H, CH_2), 2.61 (s, 3H, CH_3). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 193.24, 165.47, 155.75, 148.32, 146.78, 143.34, 140.69, 137.65, 135.89, 135.61, 130.44, 130.06, 129.87, 128.97, 128.10, 127.19, 125.50, 124.84, 123.70, 122.97, 119.42, 58.56, 26.42. Mass: *m/z*: 448.15.

4-((4-Chlorophenoxy) methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (3c): Yield: 80%, m.p.: 130-132 °C. m.f. (m.w.): $C_{15}H_{11}N_4O_3Cl$ (330.73); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 9.14 (s, 1H, triazole-H), 8.44-8.42 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.22-8.20 (d, 2H, *J* = 10.0 Hz, Ar-H), 7.35-7.32 (d, 2H, *J* = 10.0 Hz, Ar-H), 7.10-7.07 (d, 2H, *J* = 10.0 Hz, Ar-H), 5.25 (s, 2H, CH_2). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 157.36, 147.40, 144.88, 141.35, 129.91, 126.16, 125.40, 123.97, 121.31, 117.19, 61.86. Mass: *m/z*: 330.96.

1-(4-(4-((4-Chlorophenoxy) methyl)-1H-1,2,3-triazol-1-yl) phenyl) ethanone (3d): Yield: 80%, m.p.: 195-197 °C. m.f. (m.w.): $C_{17}H_{14}N_3O_2Cl$ (327.76); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 9.06 (s, 1H, triazole-H), 8.15-8.13 (d, 1H, *J* = Hz, Ar-H), 8.07-8.05 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.34-7.32 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.10-7.07 (d, 2H, *J* = 10.0 Hz, Ar-H), 5.24 (s, 2H, CH_2), 2.61 (s, 3H, CH_3). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 197.49, 157.40, 144.58, 140.09, 137.06, 130.65, 129.90, 125.36, 123.67, 120.44, 117.17, 61.91, 27.42. Mass: *m/z*: 328.65.

5-Bromo-2-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl) methoxy) benzaldehyde (3e): Yield: 45%, m.p.: 253-255 °C. m.f. (m.w.): $C_{16}H_{11}N_4O_4Br$ (403.19); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 10.34 (s, 1H, CHO), 9.22 (s, 1H, triazole-H), 8.47-8.45 (d, 1H, *J* = 6.0 Hz, Ar-H), 8.26-8.24 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.87-7.85 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.50-7.47 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.50 (s, 2H, CH_2). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 191.00, 162.60, 148.98, 144.74, 140.69, 138.51, 134.00, 130.26, 128.67, 124.75, 122.92, 121.80, 116.74, 65.63. Mass: *m/z*: 403.17 (M+), 405.12 (M+2).

5-Bromo-2-((1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl) methoxy) benzaldehyde (3f): Yield: 50%, m.p.: 235-237 °C. m.f. (m.w.): $C_{18}H_{14}BrN_3O_3$ (400.23); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 10.34 (s, 1H, CHO), 9.16 (s, 1H, triazole-H), 8.18-8.16 (d, 1H, *J* = 6.0 Hz, Ar-H), 8.12-8.10 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.87-7.86 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.49-7.47 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.64 (s, 2H, CH_2), 2.47 (s, 3H, CH_3). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 195.20, 189.30, 161.60, 148.98, 144.74, 140.69, 138.51, 134.00, 130.26, 129.67, 128.75, 124.92, 121.80, 115.54, 61.91, 28.42. Mass: *m/z*: 400.26 (M+), 402.23 (M+2).

5-Nitro-2-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl) methoxy) benzaldehyde (3g): Yield: 40%, m.p.: 242-244 °C. m.f. (m.w.): $C_{16}H_{11}N_5O_6$ (369.29); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 10.37 (s, 1H, CHO), 9.24 (s, 1H, triazole-H), 8.50-8.42 (d, 1H, *J* = 6.0 Hz, Ar-H), 8.32-8.30 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.88-7.86 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.71-7.69 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.58 (s, 2H, CH_2). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 188.54, 164.60, 148.98, 143.74, 141.69, 137.51, 132.00, 131.26, 126.67, 124.75, 123.92, 123.80, 123.74, 63.63. Mass: *m/z*: 369.45.

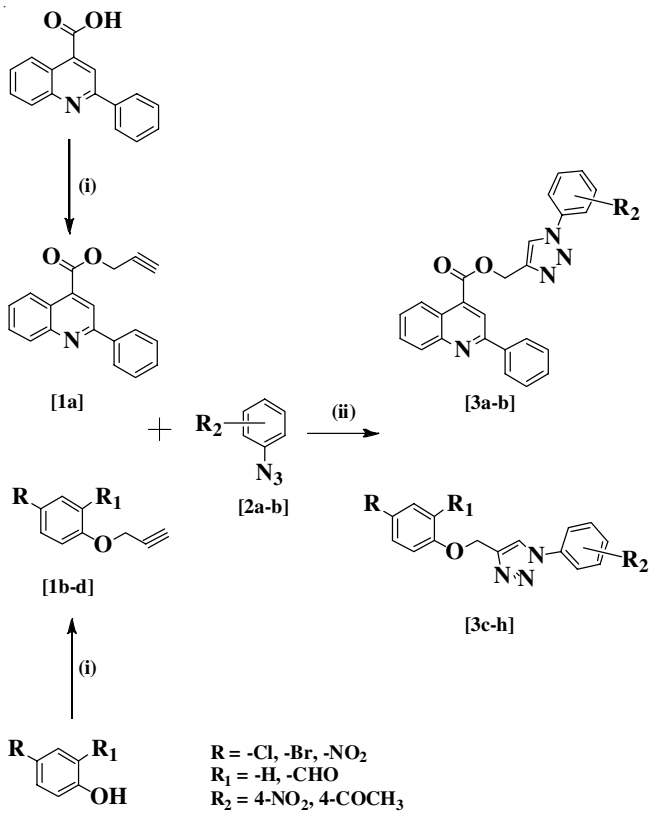
5-Nitro-2-((1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl) methoxy) benzaldehyde (3h): Yield: 45%, m.p.: 255-257 °C. m.f. (m.w.): $C_{18}H_{14}N_4O_5$ (366.33); ^{1}H NMR (400 MHz, δ ppm, DMSO-d_6): 10.37 (s, 1H, CHO), 9.21 (s, 1H, triazole-H), 8.18-8.16 (d, 1H, *J* = 6.0 Hz, Ar-H), 8.12-8.10 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.87-7.86 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.49-7.47 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.58 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR (100 MHz, δ ppm, DMSO-d_6): 193.50, 188.25, 157.36, 147.40, 144.88, 141.35, 135.69, 129.91, 126.16, 124.73, 125.40, 123.97, 121.31, 117.19, 61.86, 29.30. Mass: *m/z*: 367.24.

RESULTS AND DISCUSSION

Quinoline-4-carboxylic acid (or) 4-chloro phenol (or) 5-substituted salicyaldehyde underwent nucleophilic displacement reaction with propargyl bromide in presence of base at lab temperature to give *o*-propargylated quinoline-4-carboxylic acid (**1a**), benzene and salicyaldehyde derivatives (**1b-d**). Further, *o*-propargylated derivatives (**1a-d**) underwent Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction with substituted azido benzene derivatives (**2a-b**) at lab temperature afforded corresponding ester and ether linked 1,4-disubstituted-1,2,3-triazole derivatives (**3a-h**), respectively in good yield as depicted in **Scheme-I**. The assigned structures of the intermediates and triazole derivatives were confirmed by their physical characterization data and spectral studies *viz*. ^{1}H & ^{13}C NMR and mass analysis.

Computational evaluation of antimicrobial and anti-inflammatory activities: Prediction of activity spectra for substances (PASS) (http://www.way2drug.com/) is software for the creation of SAR models based on MNA descriptors and modified Bayesian algorithm. PASS approach can be applied to so called "drug-like" substances.

PASS programme software is used for the prediction of biological activity spectra of organic molecules on the basis of their structural formula. PASS result spectrum of a compound is designated as Probable activity (Pa) and Probable inactivity (Pi). Interpreting the prediction results is related to novelty of



Scheme-I: Synthetic route for the preparation of ester and ether linked 1,4-disubstituted 1,2,3-triazoles derivatives (**3a-h**) *via* Click approach; **Reagents and condition:** (i) Propargyl bromide, K_2CO_3, DMF, room temperature, 12-18 h; (ii) $CuSO_4{\cdot}5H_2O$, NaAs, THF-H_2O, room temperature

the analyzed compounds. For example, if Pa > 0.7, the chances of finding experimental activity are rather high but the compounds found may be close structural analogs of known drugs. If we select in the range 0.5 < Pa < 0.7, the chances for detecting experimental activity will be lower but the compounds will be less similar to known pharmaceutical agents. For Pi < Pa < 0.5, the chances of detecting experimental activity will be even lower, but if the prediction is confirmed, the compound found may prove a parent compound for a new chemical class for the biological activity examined [41]. PASS prediction of compounds **(3a-h)** were 0.22 < Pa < 0.33 in antibacterial, 0.23 < Pa < 0.35 in antifungal and 0.33 < Pa < 0.62 in anti-inflammatory (Table-1). These predictive results showed that compounds **(3a-h)** were more potent as anti-inflammatory compared to antibacterial as well as antifungal agents.

ADMETox evaluation: By applying computational methods, the various physicochemical features and pharmacokinetic descriptors were calculated through the online web tool SwissADME [42]. Whereas, *in silico* toxicity evaluation was carried out using an online server ProTox-II [43], that gives predicted oral toxicity, cytotoxicity, mutagenicity, carcinogenicity, hepatotoxicity and immunotoxicity values for 1,2,3-triazole derivatives **(3a-h)**.

Drug-likeness, bioavailability and synthetic accessibility: Drug-likeness is a quantitative parameter that measures a compound's oral bioavailability. Abbot bioavailability score predicts the chance of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 cell line permeability experiment using a model for human intestinal absorption of drugs [39]. The parameters considered to measure the score are lipophilicity (–0.7 < XLOGP3 < 5.0), molecular weight (MW) (150 g mol^{-1} < MW < 500 g mol^{-1}), polarity (20 $Å^2$ < TPSA < 130 $Å^2$), solubility (0 < log S (ESOL) < 6), saturation (0.25 < Fraction Csp^3 < 1) and flexibility (0 < of rotatable bonds < 9). This semi-quantitative rule-based score defines the compounds into four probability score classes *i.e.* 11%, 17%, 55% and 85% [44,45]. The acceptable probability score is 55% which indicates that it passed the rule of five. All the synthesized compounds **(3a-h)** showed a score of 55%, indicating good bioavailability (Table-2).

The drug-likeness scores were also calculated by considering (miLog P, TPSA, nAtoms, nON, nOHNH, rotb & MW) based on Lipinski's, Ghose and Veber rule for the prediction of bioactivity score were carried out. The results of these prediction showed that the compounds obeyed Lipinski's, Ghose and Veber rule except compound **(3g)** which violates Veber rule (Table-3). Further, synthetic accessibility of the **(3a-h)** was assessed to quantify the complexity of the molecular structure. The results showed that the score were in the range of 2.53-3.38 revealed that the compounds does not have complex synthetic route as tabulated in Table-3.

The compound's aqueous and non-aqueous solubility influences the absorption and is an important factor in view of the drug development process. Lipophilicity is the effective solubility of a compound into the non-aqueous medium and correlated to various models of drug properties such as adsorption, distribution, metabolism and toxicity. The mean predicted

TABLE-1
PREDICTED BIOLOGICAL ACTIVITY OF SYNTHESIZED COMPOUNDS (**3a-h**)

Compound	Antibacterial		Antifungal		Anti-inflammatory	
	Probable to be active (Pa)	Probable to be inactive (Pi)	Probable to be active (Pa)	Probable to be inactive (Pi)	Probable to be active (Pa)	Probable to be inactive (Pi)
3a	0.297	0.061	–	–	0.524	0.050
3b	0.264	0.076	–	–	0.622	0.027
3c	0.257	0.079	0.236	0.114	0.501	0.056
3d	0.219	0.102	0.235	0.115	0.610	0.029
3e	0.317	0.054	0.356	0.061	–	–
3f	0.281	0.067	0.359	0.060	0.332	0.135
3g	0.326	0.051	0.303	0.080	0.342	0.127
3h	0.328	0.050	0.329	0.070	0.382	0.105

TABLE-2
PHYSICO-CHEMICAL PROPERTIES OF SYNTHESIZED COMPOUNDS (**3a-h**)

Compound	m.f.	m.w.	XLOGP3	Fraction Csp^3	log S (ESOL)
3a	$C_{16}H_{11}N_5O_6$	369.29	1.97	0.06	-3.37
3b	$C_{18}H_{14}N_4O_5$	366.33	1.82	0.11	-3.26
3c	$C_{15}H_{11}N_4O_3Cl$	330.73	3.30	0.07	-4.19
3d	$C_{17}H_{14}N_3O_2Cl$	327.76	3.16	0.12	-4.08
3e	$C_{16}H_{11}N_4O_4Br$	403.19	2.83	0.06	-4.23
3f	$C_{18}H_{14}N_3O_3Br$	400.23	2.69	0.11	-4.12
3g	$C_{25}H_{17}N_5O_4$	451.43	4.49	0.04	-5.59
3h	$C_{27}H_{20}N_4O_3$	448.47	4.34	0.07	-5.48

TABLE-3
DRUG LIKENESS, BIOACTIVITY AND SYNTHETIC ACCESSIBILITY SCORE OF SYNTHESIZED COMPOUNDS (**3a-h**)

Compound	Lipinski	Ghose	Veber	Bioactivity score	Synthetic accessibility
3a	Yes	Yes	Yes	0.55	3.35
3b	Yes	Yes	Yes	0.55	3.38
3c	Yes	Yes	Yes	0.55	2.63
3d	Yes	Yes	Yes	0.55	2.53
3e	Yes	Yes	Yes	0.55	2.79
3f	Yes	Yes	Yes	0.55	2.78
3g	Yes	Yes	No	0.55	2.81
3h	Yes	Yes	Yes	0.55	2.86

TABLE-4
PREDICTED ABSORPTION PARAMETERS OF SYNTHESIZED COMPOUNDS (**3a-h**)

Compound	Consensus log Po/w	Consensus log S	Solubility class
3a	3.58	-5.59	Moderately soluble
3b	4.14	-5.48	Moderately soluble
3c	2.41	-4.19	Moderately soluble
3d	3.16	-4.08	Moderately soluble
3e	2.23	-4.23	Moderately soluble
3f	2.96	-4.12	Moderately soluble
3g	1.00	-3.37	Soluble
3h	1.60	-3.26	Soluble

lipophilicity values are known as the consensus log Po/w is used to decide the non-aqueous solubility. A molecule is more soluble if the consensus log Po/w values is more negative. Results showed that compounds **(3a-h)** were not soluble in non-aqueous medium (Table-4). Some drugs have to be highly water solubility to deliver active ingredient and to estimate this qualitative estimation of solubility log S scale was used: if log S < –10 poorly soluble, < –6 moderately soluble, < –4 soluble, < –2 very soluble and < 0 highly soluble. Based from this predictive model, compounds **(3a-f)** were predicted to be moderately soluble and compounds **(3g-h)** are predicted to be water soluble (Table-4).

After absorption of drug by the system, it encounters various membrane barriers such as hepatocyte membrane, gastrointestinal epithelial cells, blood capillary wall, glomerulus, restrictive organ barriers (*e.g.* blood-brain-barrier) and the target cell. The brain or intestinal estimated permeation method (BOILED-Egg) is proposed as an accurate predictive model that works by computing the lipophilicity and polarity of small molecules. The white region indicates passive gastrointestinal absorption and yellow region indicates passive brain permeation. The derivatives **(3a)** and **(3g)** have low GI absorption as shown in Fig. 1, while compounds **(3d)** and **(3f)** have BBB permeant as tabulated in Table-5. A compound being blood-brain permeant there is a possibility of causing harmful toxicants in the brain and blood stream when metabolized. The remaining compounds were predicted to be non blood-brain penetrates. A molecule is said to be less skin permeant if the

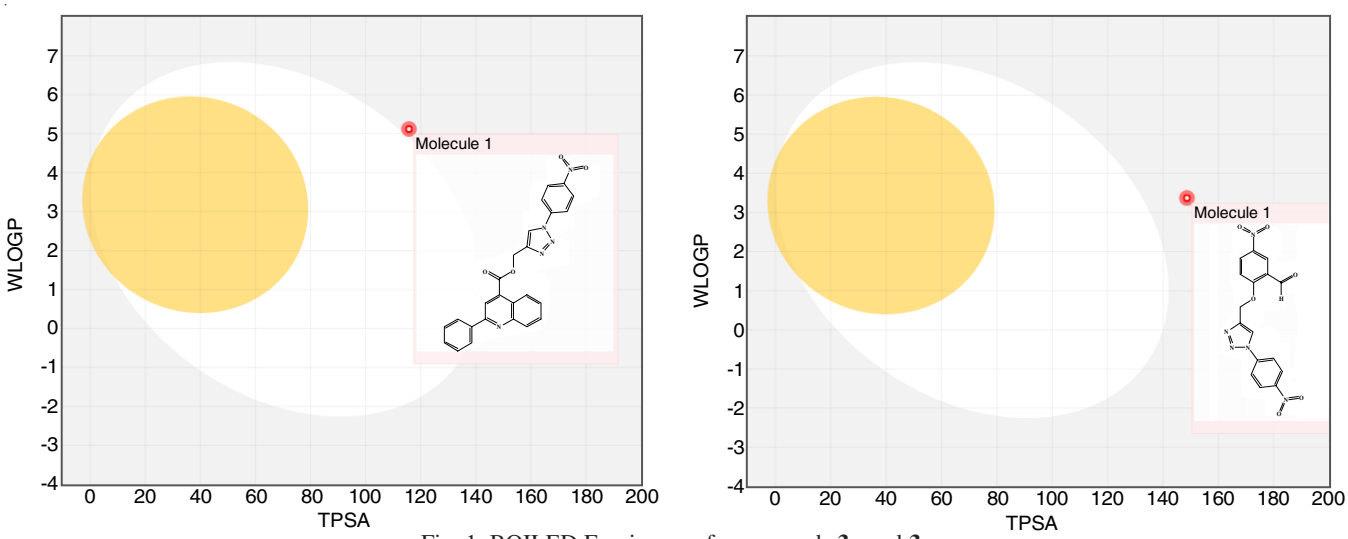


Fig. 1. BOILED Egg image of compounds **3a** and **3g**

TABLE-5
PREDICTED DISTRIBUTION
PARAMETERS OF THE COMPOUNDS (**3a-h**)

Compound	GI absorption	BBB permeant	log Kp (cm/s)
3a	Low	No	-5.87
3b	High	No	-5.95
3c	High	No	-5.97
3d	High	Yes	-6.06
3e	High	No	-6.75
3f	High	Yes	-6.83
3g	Low	No	-7.15
3h	High	No	-7.24

value of log Kp is more negative. From the predicted results, compounds **(3g)** and **(3h)** were found to be the least skin permeant (Table-5).

Metabolism plays an important role in the bioavailability of drugs as well as drug-drug interactions. It is also important to have a better understanding if a certain compound is a substrate or non-substrate of the certain proteins. The permeability glycoprotein (P-gp) is an important protein in assessing active efflux through biological membranes and cytochrome P450 (CYP) enzymes as they involved in drug elimination through metabolic transformation. Both these can process small molecules synergistically to enhance the protection of tissues and organisms. Inhibition of these isoenzymes may result in unwanted adverse side-effects by lowering the solubility and the accumulation of the drug or its metabolites. Hence the compounds **(3a-h)** were evaluated to determine whether the compound can act as substrate or an inhibitor of P-gp and CYPs. All compounds are found to be non-substrates of P-gp. The compounds **(3c-f)** presented were found to be substrates of CYP1A2. All compounds are predicted to be substrates of CYP2C19 and CYP2C19. All compounds are predicted to be CYP2D6 non substrates and the compounds **3b**, **3e** and **3h** were found to be potential substrates for CYP3A4 (Table-6).

Toxicity evaluation is initially used to determine the compound's toxicity as a fast and an inexpensive method to reduce the number of compounds to be sent later for further testing. *in silico* toxicity evaluation could not act as absolute answer for the compound's toxicity evaluation and it should always be accompanied by *in vitro* and *in vivo* experiments to verify the biological activities beyond the capability of these computational approaches. Here, the synthesized compounds were subjected to an *in silico* toxicity evaluation using Pro-Tox. The LD_{50} is defined as the median lethal dose of a compound at which the test subjects die upon exposure to it [38]. The toxicity class ranges from 1 to 6 as shown below:

Class I: fatal if swallowed ($LD_{50} \leq 5$)
Class II: fatal if swallowed ($5 < LD_{50} \leq 50$)
Class III: toxic if swallowed ($50 < LD_{50} \leq 300$)
Class IV: harmful if swallowed ($300 < LD_{50} \leq 2000$)
Class V: may be harmful if swallowed ($2000 < LD_{50} \leq 5000$)
Class VI: non-toxic ($LD_{50} > 5000$)

The results showed that the synthesized compounds were predicted to be harmful if swallowed and belongs to class IV (Table-7).

TABLE-7
PREDICTED LD_{50} AND TOXICITY
CLASS OF THE COMPOUNDS (**3a-h**)

Compound	Predicted LD_{50} (mg/kg)	Toxicity class
3a	495	4
3b	495	4
3c	494	4
3d	400	4
3e	494	4
3f	1000	4
3g	494	4
3h	400	4

The ProTox online server also predicts four toxicological endpoints such as cytotoxicity, mutagenicity, carcinogenicity and immunotoxicity. Results suggested that all the compounds were predicted to be non-immunotoxic (Table-8). Immunotoxic chemicals are known to alter the correct functioning of immune system by B cell growth inhibition. Moreover, the organ toxicity, specifically hepatotoxicity was predicted to evaluate if the compound will cause liver dysfunction. Results showed that the compounds **(3a-d)** were non-hepatotoxic and remaining compounds **(3e-f)** are hepatotoxic. Moreover, compounds **(3a-c), (3e)** and **(3g-h)** were predicted to be a mutagenic compound (Table-8). This means that it can possibly cause alteration of a genetic material, such as the DNA of an organism [42].

Conclusion

In the present investigation, synthesis of pharmacophoric units (quinoline and 1,2,3-triazole) linked through ester and (substituted aromatic ring and 1,2,3-triazole) linked through an ether were carried out in good yield. The assigned structures

TABLE-6
PREDICTED METABOLISM PARAMETERS OF THE COMPOUNDS (**3a-h**)

Compound	P-gp	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
3a	No	No	Yes	Yes	No	No
3b	No	No	Yes	Yes	No	Yes
3c	No	Yes	Yes	Yes	No	No
3d	No	Yes	Yes	Yes	No	No
3e	No	Yes	Yes	Yes	No	Yes
3f	No	Yes	Yes	Yes	No	No
3g	No	No	Yes	Yes	No	No
3h	No	No	Yes	Yes	No	Yes

TABLE-8
PREDICTED ACTIVITY OF THE COMPOUNDS ON TOXICITY ENDPOINTS (**3a-h**)

Compound	Hepatotoxicity	Carcinogencity	Immunotoxicity	Mutagencity	Cytotoxicity
3a	Inactive	Active	Inactive	Active	Inactive
3b	Inactive	Inactive	Inactive	Active	Inactive
3c	Inactive	Active	Inactive	Active	Inactive
3d	Inactive	Inactive	Inactive	Inactive	Inactive
3e	Active	Active	Inactive	Active	Active
3f	Active	Inactive	Inactive	Inactive	Inactive
3g	Active	Active	Inactive	Active	Inactive
3h	Active	Active	Inactive	Active	Inactive

of the compound were confirmed by multi nuclear NMR (^{1}H & ^{13}C) and Mass spectrometry. PASS prediction of the compounds **(3a-h)** showed that the compounds are more potent as anti-inflammatory compared to antibacterial which in turn more potent than antifungal agents. Furthermore, these compounds were subjected to *in silico* ADMETox evaluation. All the compounds were found to pass the ADME evaluation and few compounds passed the predicted toxicity evaluation. From this work an initial approach in identifying potential novel molecules with promising activity with low toxicity was carried out and paves the way for further investigation and development.

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CONFLICT OF INTEREST

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

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