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Synthesis of Substituted 1,2,4-Triazole Containing Novel Small Molecules by Using Microwave

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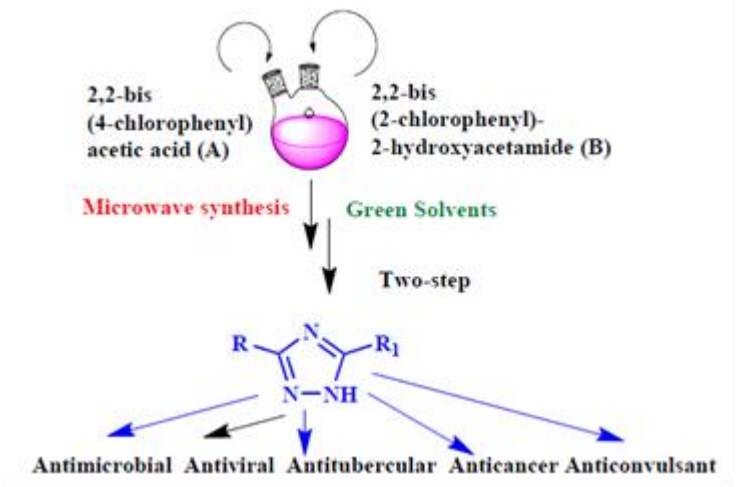
Abstract

Green chemistry finds its most promising use in the synthesis of compounds using ecologically friendly, non-hazardous, non-irritant, gentle, and reproducible catalysts and solvents. The adoption of green chemistry approaches has recently been shown to significantly reduce chemical waste and reaction times in a number of organic synthesis processes. The objective of this research work is to develop an eco-friendly method for the synthesis of substituted 1,2,4-triazole containing novel small molecules. The approach makes use of acid as starting material on reaction with hydrazine forms Acetyl-hydrazide. On condensation with nitrile and subsequent ring closure forms substituted 1,2,4-Triazole derivatives. This research work describes the synthesis of thirty-two unique 1,2,4-triazole containing novel small molecules. It has been shown that this technique is superior to other synthetic methods in terms of reaction time, yield, and energy efficiency along with use of green chemistry and microwave.



1. Introduction

Synthesis of new compounds is essential part of drug development. The structure's molecular framework describes different binding areas that make it unique, powerful, and selective for a range of biological targets [1]. In open-chain and cyclic structures, heteroatoms act as isosteric or bio-isosteric substitutes for carbon or carbon substructures. In the fields of organic and medicinal chemistry, they have been regarded as favored structures. The fact that they constitute a crucial component of many compounds with biological activity illustrates the importance of heterocycles in contemporary medication development [2,3]. 1,2,4-triazole derivatives are examples of such a flexible heterocyclic pharmacophore due to its drug-like and adaptable binding capabilities. 1,2,4-triazole has molecular formula of $C_2H_3N_3$ and molecular weight of 69.07gm/mol. In the five-membered ring, a maximum of two types of positional arrangement of nitrogen atoms led to the formation of two substantial isomers, namely, 1,2,4-triazole (ν-1,2,4-triazole) and 1,2,4-triazole (s-1,2,4-triazole). Each of them shows mainly two tautomers depending on the hydrogen bonded to ring nitrogen [4,5]. Both the 1,2,4-triazoles and their derivatives have significant biological properties including antimicrobial, antiviral, antitubercular, anticancer, anticonvulsant, analgesic, antioxidant, anti-inflammatory, and antidepressant activities (Fig. 1) [6]. The aim of producing new powerful small molecules is to have novel therapeutic heterocyclic hybrid molecules in which two or more bioactive scaffolds are encapsulated inside a single molecule to perform multiple or combination biological activities [7-9].

Many approaches for synthesis of 1,2,4-triazole are employed like metal-free click synthesis reported by Thomas and team where primary amines, enolizable ketones, and 4-nitrophenyl azide in the acetic acid catalyst (30 mol%) are heated at 100°C in toluene [10]. Other methods include organocatalytic 1,3-dipolar cycloaddition reaction [11,12] and microwave irradiation were applied for the copper-catalyzed azide–alkyne cycloaddition method [13-15].

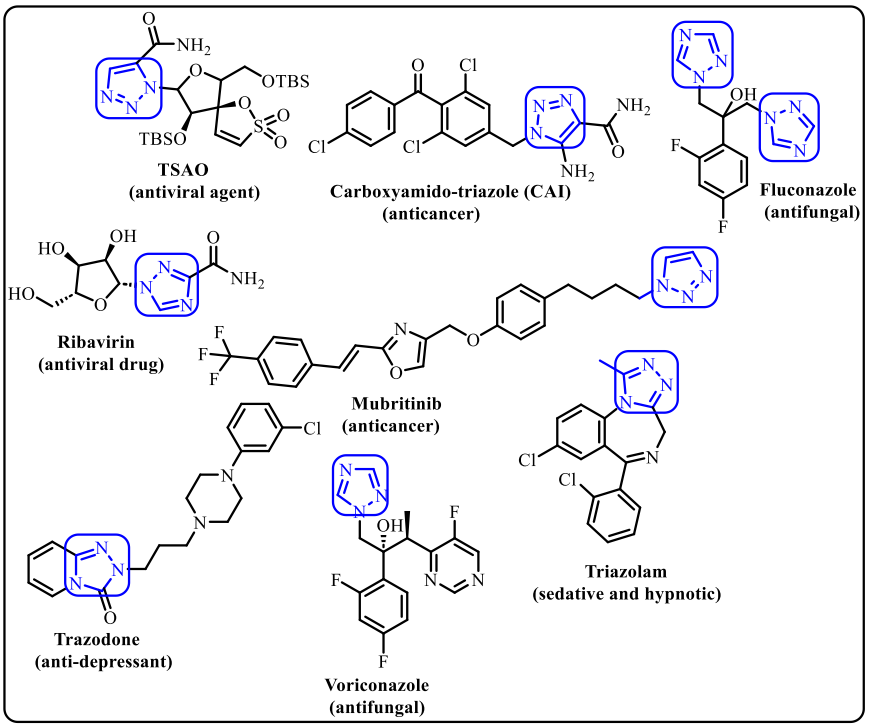


Fig. 1 *2D structures of marketed drugs containing 1,2,4-triazole [16-19]*

2. Materials and Method

2.1 Experimental

All the chemicals and reagents/solvents were obtained from the commercial suppliers with the high purity. The chemicals and reagents/solvents were used as received without further purification. 1200 W quartz heater containing microwave was used for the microwave assisted synthesis. Melting points of all compounds were determined in one-end open capillary tubes on a liquid paraffin bath and are uncorrected. The ^{1}H spectra were recorded in DMSO, using a Bruker 400 MHz FT-NMR Spectrometer Avance III, the solvents and reagents were used without further purification. General scheme for the synthesis of substituted 1,2,4-triazole, starting from

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the acid has been shown below in Fig. 2. The substituted pattern for the series-1, 2 & 3 has been given below (Table 1) to the general chemical scheme.

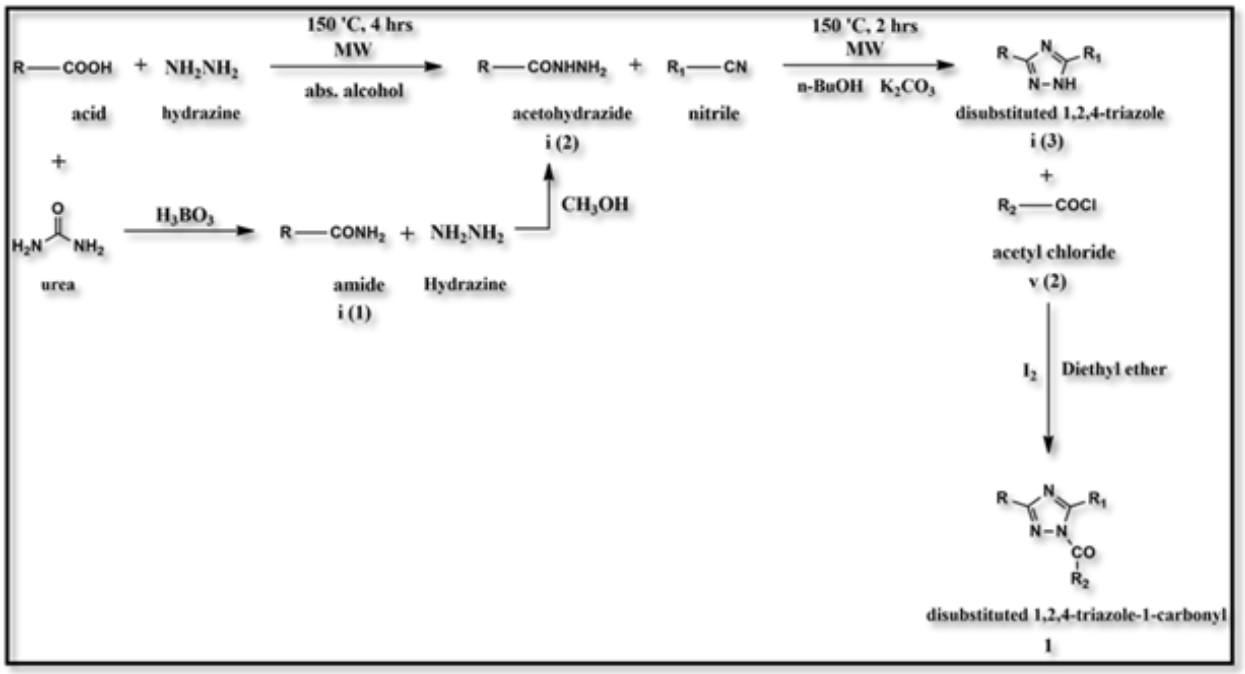
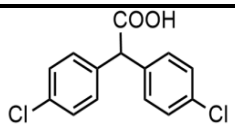
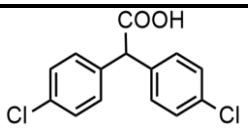
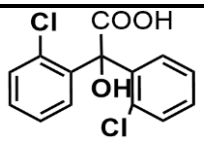
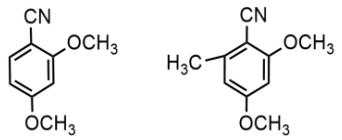
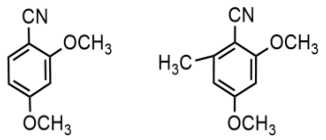
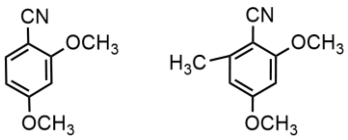
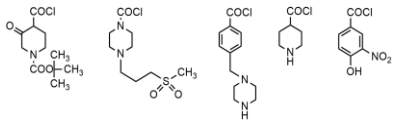
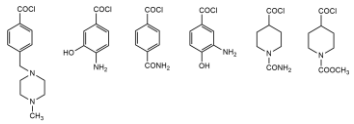
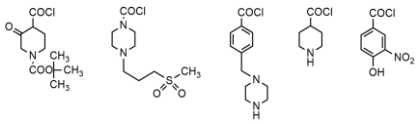


Fig. 2 *Scheme for the synthesis of disubstituted 1,2,4-triazole*

Table 1 *Substituted pattern for the series-1, 2 & 3*

	Series-1	Series-2	Series-3
R			
R_1			
R_2			

2.1.1 General Synthetic Procedure

(a) Step 1: Amide (i (1)) from Acid (Greener Method) **[20]**

Carboxylic acid (0.89 g), urea (g of acid x 1.5) and boric acid (g of acid x 0.4) was weighed. The weighed amount was thoroughly mixed and triturated in mortar and pestle for 2-5 min. The triturated mixture was then transferred into the beaker and was directly heated without the solvent at the 160-180 °C for 10-30 min. During the course of reaction, the reaction mixture was completely melted and then reappeared as product (amide). Heating was removed and product (amide) was allowed to cool to room temperature. The aqueous ammonia solution (50-55 ml) was added to the crude product and heated with stirring, so unreacted acid was removed. Heating was stopped and filter to give a product. The collected product (amide) was successively washed with distilled water (100 ml) to remove residual boric acid and product was dried at room temperature to give a corresponding amide (i (1)) with high purity.

(b) Step 2: Hydrazide (i (2)) from Amide (i (1)) **[21]**

19.39 g of amide (i (1)) was dissolved in 39.48 g of methyl alcohol and 14.14 g of hydrazine hydrate (100 %) was added to it. The reaction mixture was refluxed in glycerine bath for 4 hours at 110°C. After which alcohol was

distilled off and solid mass, acid hydrazide was taken out in hot condition. Cool the product, which afford the acid hydrazide (i (2)).

(c) Step 2: Hydrazide (i (2)) from Acid (Microwave Method) **[22]**

The aromatic hydrazides were prepared in a single step from the carboxylic acid precursor by using microwave irradiation. 9.7 g of amide was dissolved in 19.5 g of absolute alcohol and 4.13 g of hydrazine hydrate (100 %) were added to a 20 mL microwave reaction vessel. The reaction mixture was subjected to microwave irradiation at 150 °C for 4 hours. This gives the respective hydrazide; this hydrazide was isolated by standard aqueous workup. The crude product was found to be pure enough to be carried on to the 1,2,4-triazole formation step.

(d) Step 3: 1,2,4-Triazole (i (3)) from Condensation of Hydrazide (i (2)) and Nitrile **[23]**

Aromatic hydrazide (i (2)) (0.005 moles) and substituted nitrile (0.0055 moles) were added to a 20 mL microwave reaction vessel with 10 mL of n-Butanol. Potassium carbonate (0.0055 moles) was added and the reaction mixture was subjected to microwave irradiation at 150°C for 2 hours. Precipitated substituted 1,2,4-triazole (i (3)) was filtered after cooling the reaction mixture and recrystallized from ethanol.

In all cases, product 1,2,4-triazoles (i (3)) were insoluble in n-butanol leading to easy recoveries by filtration. Isolated crude materials could then be recrystallized in ethanol to give analytically pure products.

(e) Step 4: N-Acylation to Give Final Product (1) **[24]**

5 g (0.038 mol, 1.5 eqv.) of sodium acetate trihydrate was dissolved in 50 ml of brine solution (36 % aq. Solution of sodium chloride). To this was added 0.025 mol of the substituted 1,2,4-triazole (i (3)) dissolved in the water (water insoluble 1,2,4-triazole were taken in 20 ml acetone). Then 2 ml of acetyl chloride (v (2)) (0.028 mol, 1.1 eqv.) in 3 ml of acetone was added to the mixture drop-wise with stirring at room temperature. The reaction mixture was stirred for further one hour. Saturated $NaHCO_3$ solution was added till the effervescence ceased. The solution was then acidified with conc. HCl. The sparingly soluble acetyl derivative separated as solid. It was filtered under suction, crystallized from methanol/methanol–water solvent system. This affords the final compound (1).

(f) Acetyl Chloride (v (2)) from Acid (v (1)) **[25]**

To 100 g of acid (v (1)) in round bottom flask connected with a condenser, 80 g of phosphorus trichloride are added through a dropping funnel. Hydrochloric acid gas appears and the reaction rate is regulated by cooling the reaction mixture with cold water. After all phosphorus trichloride has been added the reaction flask is gently heated to 40-50° C and the liquid (reaction mixture), which was homogeneous before heating separates into two layers. Acetyl chloride (v (2)) which forms the upper, lighter layer, and lower heavier layer is of phosphorous acid. The mixture is heated until nothing more passes over the two layers. After the completion of the reaction, distilled the reaction mixture to isolate acetyl chloride. The first collected portion (upper layer of the reaction mixture) of the distillate was acetyl chloride (v (2)). Since acetyl chloride is very easily decomposed by moisture, the distillate must be protected from the air with a calcium chloride tube. For complete purification of crude acetyl chloride (v (2)), the distillate is redistilled. Polar tail of the final compound-1 was synthesized from the acid. Fig. 3 contains the method of polar tail synthesis.

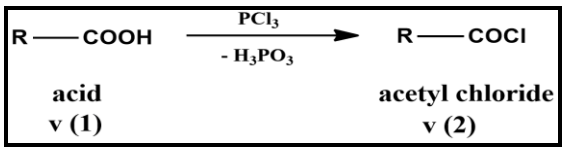


Fig. 3 *Scheme for the synthesis of acetyl chloride from acid*

2.2 Series-1

2.2.1 Compound Structure

As shown in Fig. 4, there are total 10 compounds (disubstituted 1,2,4-triazole) in series-1. All the compounds were synthesized by using the different substitution pattern for R, R_1 and R_2.

2.2.2 Compound Characterization

(a) Starting Material

Crystalline white. IR (KBr): 3018.70 (Ar, C-H), 1699.34 (COOH, C=O), 1494.88 (Ar, C=C), 698.25 (C-Cl) cm-1

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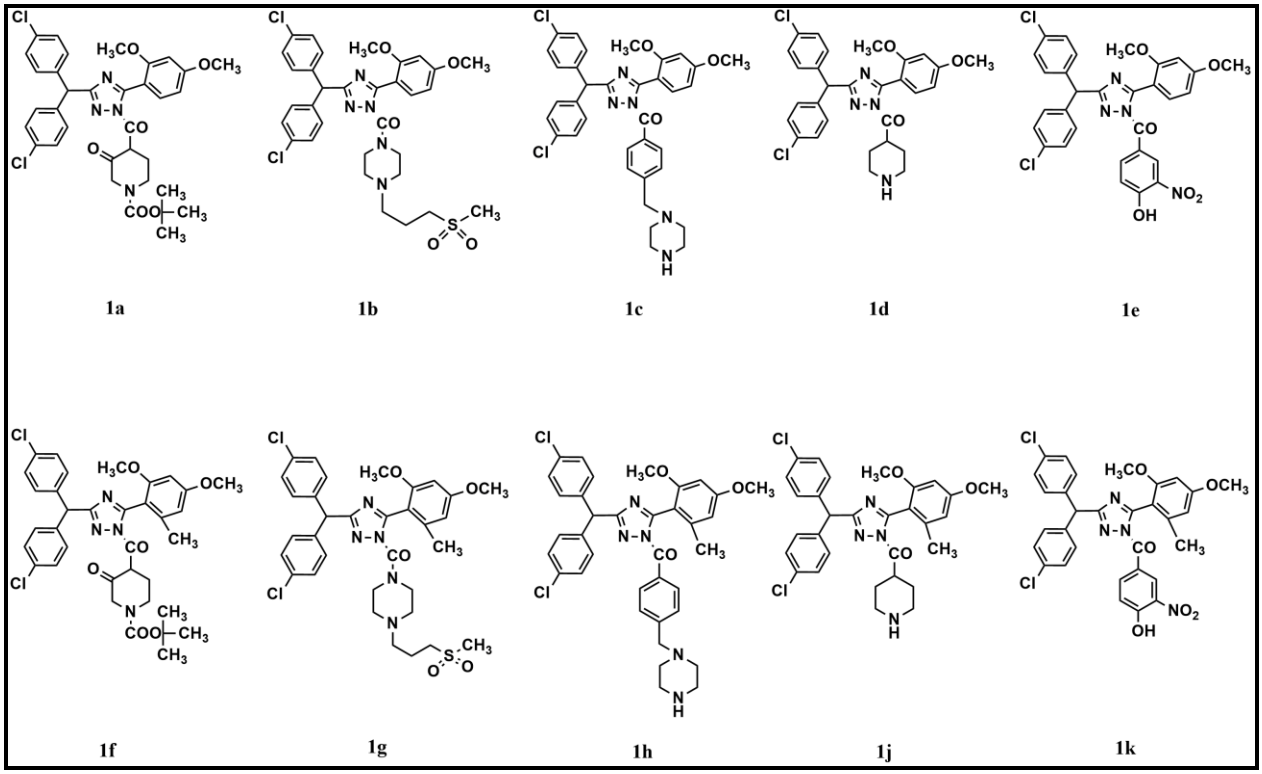

Fig. 4 *Structures of the compounds from Series-1*

(b) Compound 1a

Amorphous white. 86 % yield, m.p. 262-264 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70: 30 v/v) Rf: 0.67, IR (KBr): 3278.13 (Ar, C-H), 1725.38 (COO, C=O), 1696.45 (C=O), 1621.22 (Ar, C=N), 1423.51 (Ar, C=C), 1239.31 (Ar, C-N), 843.88 (C-Cl) cm^{-1}, ^1H NMR (400 MHz, DMSO) δ_H (ppm): 2.568 (09H, side chain CH3), 3.374 (06H, OCH3), 3.792 (07H, side chain Ar-H), 5.562 (01H, CH), 6.556-6.562, 7.063 (03H, Ar-H), 7.063-7.604 (08H, Ar-H), MS (EI, 70 eV) m/z: 666.21 [M+1]+, 531.19, 427.17, 402.22, 263.03

(c) Compound 1b

White. 82 % yield, m.p. 265-267 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70: 30 v/v) Rf : 0.70, IR (KBr): 2983.98 (CH3, C-H), 1696.45 (C=O), 1618.33 (Ar, C=N), 1243.16 (Ar, C-N), 1145.75 (SO2, S=O), 1057.99 (C-S) cm-1, ^1H NMR (400 MHz, DMSO) δ_H (ppm): 2.353 (09H, side chain CH3), 2.893 (08H, side chain Ar-H), 3.490-3.831 (06H, OCH3), 5.338 (01H, CH), 6.647 (03H, Ar-H), 7.083-7.579 (08H, Ar-H), MS (EI, 70 eV) m/z: 673.11 [M+1]+, 359.4, 341.4, 331.4, 313.5

(d) Compound 1c

Light purple. 74 % yield, m.p. 260-263 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70 : 30 v/v) Rf : 0.76, IR (KBr): 3337.93 (Ar, C-H), 1688.73 (Ar, C=N), 1576.86 (Ar, N-H), 1230.63 (Ar, C-N) cm-1, 1H NMR (400 MHz, DMSO) δH (ppm): 1.287 (01H, NH), 2.443 (08H, side chain Ar-H), 2.792 (06H, OCH3), 3.470 (02H, side chain CH), 5.438 (1H, CH), 6.558-6.571, 7.090 (03H, Ar-H), 7.067-7.077 (08H, Ar-H), 7.601-7.929 (04H, side chain Ar-H), MS (EI, 70 eV) m/z: 641.18 [M−1]-, 541.08, 485.01, 327.10, 233.09, 204.03

(e) Compound 1d

Purple. 79 % yield, m.p. 239-242 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70 : 30 v/v) Rf : 0.72, IR (KBr): 1729.24 (C=O), 1696.45 (Ar, N-H), 1620.26 (Ar, C=N), 1235.45 (Ar, C-N) cm-1, 1H NMR (400 MHz, DMSO) δH (ppm): 1.329-1.647 (04H, side chain Ar-H), 2.010 (01H, NH), 2.324-2.710 (05H, side chain Ar-H), 2.853 (06H, OCH3), 4.593 (01H, CH), 6.793-7.055 (03H, Ar-H), 7.061-7.536 (08H, Ar-H), MS (EI, 70 eV) m/z: 551.17 [M]+, 433.12, 313.16, 274.16, 135.01

(f) Compound 1e

Yellow. 68 % yield, m.p. 246-249 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70 : 30 v/v) Rf : 0.66, IR (KBr): 3332.14 (Ar, O-H), 1696.45 (Ar, C=N), 1220.02 (NO2, N-O) cm-1, 1H NMR (400 MHz, DMSO) δH (ppm): 2.439-2.848 (06H, OCH3), 5.721-5.738 (01H, CH), 5.765-5.785 (01H, OH), 6.810-6.848 (03H, Ar-H), 7.083-7.278 (08H, Ar-H), 7.580-7.587 (03H, side chain Ar-H), MS (EI, 70 eV) m/z: 606.10 [M+1]+, 536.12, 408.19

(g) Compound 1f

Off white. 81 % yield, m.p. 279-281 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70 : 30 v/v) Rf : 0.69, IR (KBr): 3090.07 (CH3, C-H), 1614.47 (COO, C=O), 1518.99 (Ar, C=N), 1380.11 (Ar, C-N) cm-1, 1H NMR (400 MHz, CDCl3) δH (ppm): 0.925 (04H, side chain Ar-H), 1.337 (09H, side chain CH3), 2.360 (03H, CH3), 2.759 (06H, OCH3), 3.352 (03H, side chain Ar-H), 5.746 (01H, CH), 7.049-7.884 (08H, Ar-H), 7.951-8.162 (02H, Ar-H), MS (EI, 70 eV) m/z: 679.18 [M]+, 678.12 [M–1]+, 533.10, 501.06

(h) Compound 1g

Pale yellow. 75 % yield, m.p. 302-305 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70 : 30 v/v) Rf : 0.74, IR (KBr): 2891.39 (CH3, C-H), 1694.52 (Ar, C=N), 1318.39 (Ar, C-N), 1166.97 (SO2, S=O), 1030.99 (C-S) cm-1, 1H NMR (400 MHz, CDCl3) δH (ppm): 1.177-1.196 (05H, side chain CH2), 2.016 (03H, side chain Ar-H), 2.513-2.531 (06H, OCH3), 3.357 (01 H, side chain CH2), 3.357 (03 H, CH3), 3.573 (04H, side chain Ar-H), 4.139 (03H, side chain CH3), 4.165 (01H, side chain Ar-H), 5.535 (01H, CH), 6.771-6.793 (02H, Ar-H), 7.055-7.654 (08H, Ar-H), MS (EI, 70 eV) m/z: 686.17 [M]+, 649.16, 541.10, 529.08, 426.16, 361,02

(i) Compound 1h

Light purple. 69 % yield, m.p. 264-267 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70 : 30 v/v) Rf : 0.65, IR (KBr): 3029.31 (Ar, C-H), 2846.06 (CH3, C-H), 1692.59 (Ar, C=N), 1560.46 (Ar, N-H), 1301.03 (Ar, C-N) cm-1, 1H NMR (400 MHz, CDCl3) δH (ppm): 1.278 (01H, NH), 1.995-2.504 (04H, side chain Ar-H), 2.573 (06H, OCH3), 3.357 (03H, CH3), 3.573 (04H, side chain Ar-H), 4.139-4.165 (02H, CH2), 5.535 (01H, CH), 6.771-6.793 (02H, Ar-H), 7.055-7.276 (08H, Ar-H), 7.282 (02H, side chain Ar-H), 9.073 (02H, side chain Ar-H), MS (EI, 70 eV) m/z: 657.17 [M+1]+, 658.22 [M+2]+, 569.12, 533.08, 488.13, 231.12

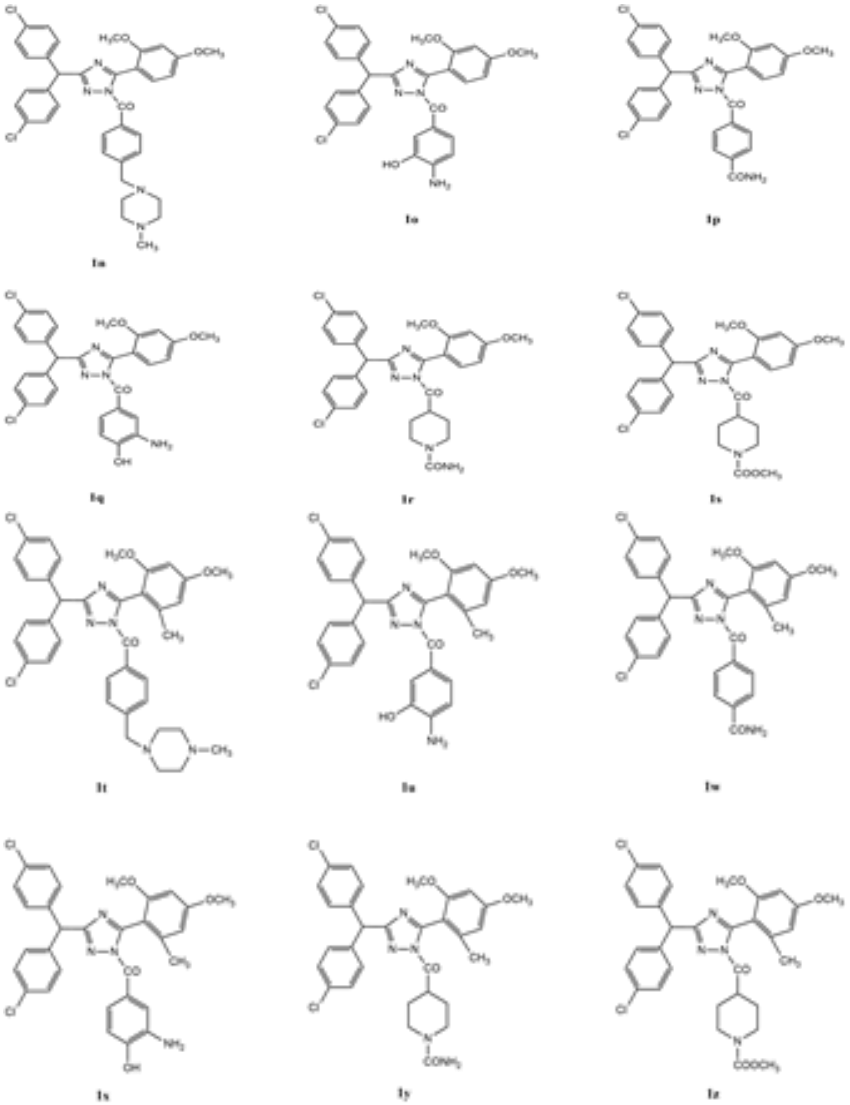

Fig. 5 *Structures of the compounds from Series-2*

(j) Compound 1j

Light purple. 71 % yield, m.p. 254-256 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70: 30 v/v) Rf : 0.73, IR (KBr): 2756.97 (CH3, C-H), 1524.78 (Ar, N-H), 1329.96 (Ar, C-N) cm-1, 1H NMR (400 MHz, DMSO) δH (ppm): 0.947 (01H, NH), 1.495 (03H, CH3), 1.495 (01H, side chain Ar-H), 2.395 (05H, side chain Ar-H), 2.873 (06H, OCH3), 3.441 (03H, side chain Ar-H), 5.746 (01H, CH), 7.092 (02H, Ar-H), 7.143-7.951 (05H, Ar-H), 8.136-8.162 (03H, Ar-H), MS (EI, 70 eV) m/z: 565.13 [M]+, 522.14, 485.17, 380.02

(k) Compound 1k

Yellow. 77 % yield, m.p. 257-259 °C (lit), TLC (eluent: n-Hexane/ethyl acetate. 70: 30 v/v) Rf : 0.70, IR (KBr): 3448.84 (Ar, O-H), 2914.54 (CH3, C-H), 1540.21 (NO2, N-O) cm-1, 1H NMR (400 MHz, CDCl3) δH (ppm): 2.406 (03H, CH3), 2.725 (06H, OCH3), 4.588 (01H, OH), 4.588 (01H, CH), 7.057-7.063 (02H, Ar-H), 7.073-7.284 (08H, Ar-H), 7.515-7,531 (03H, side chain Ar-H), MS (EI, 70 eV) m/z: 618.16 [M-1]-, 604.01, 541.16

2.3 Series-2

2.3.1 Compound Structure

As shown in Fig. 5, there are total 12 compounds (disubstituted 1,2,4-triazole) in series-2. All the compounds were synthesized by using the different substitution pattern for R, R_1 and R_2.

2.3.2 Compound Characterization

Physical characteristics of compounds (series-2) has been given in the Table 2.

Table 2 *Physical characteristics of the compounds from Series-2*

Compound	Molecular Weight	% Yield	M. P	Rf
1n	656.60	62	275-278	0.67
1o	575.44	68	232-235	0.66
1p	587.45	56	235-237	0.71
1q	575.44	59	230-232	0.64
1r	594.49	61	241-244	0.73
1s	609.50	66	248-250	0.61
1t	670.63	72	281-283	0.59
1u	589.47	63	238-241	0.63
1w	601.48	73	243-245	0.70
1x	589.47	60	240-242	0.72
1y	608.51	67	246-249	0.58
1z	623.53	55	251-253	0.67

2.4 Series-3

2.4.1 Compound Structure

As shown in Fig. 6, there are total ten compounds (disubstituted 1,2,4-triazole) in series-3. All the compounds were synthesized by using the different substitution pattern for R, R_1 and R_2.

3. Results and Discussion

The current approach is flexible and supports many different substitution patterns. An enhanced synthetic process was utilized in the production of a small library consisting of thirty-two substituted derivatives of 1,2,4-triazole.

3.1 Route of Synthesis for Lead Compound 1a

Synthesis of final compounds was carried out by condensation of 1,2,4-triazole derivative with polar tail, in the presence of PCl3 and I2. Polar tail v (2) was synthesized from the reaction of acid with PCl3. Polar tail synthesis was problematic as it involves the I2 and PCl3.

Compounds i (1) to i (3) were obtained as intermediates in the synthesis of final compounds. A novel solvent free green chemistry-based method for the synthesis of amide is developed, from the acid and urea in the presence of boric acid.

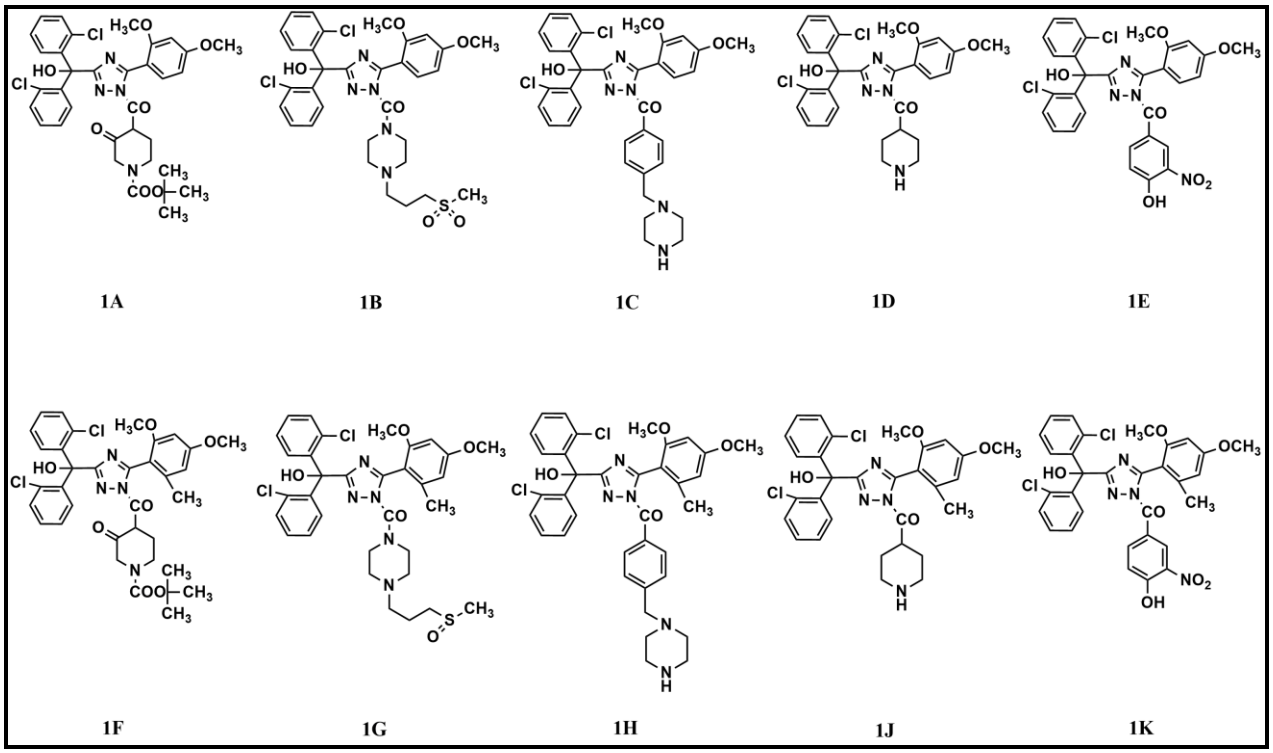

Fig. 6 *Structures of the compounds from Series-3*

3.1.1 Compound Characterization

Physical characteristics of compounds (series-3) has been given in the Table 3.

Table 3 *Physical characteristics of the compounds from Series-3*

Compound	Molecular Weight	% Yield	M. P	Rf
1A	681.56	78	290-293	0.76
1B	688.62	73	296-298	0.75
1C	658.57	79	277-280	0.68
1D	567.46	65	241-243	0.66
1E	621.42	72	260-262	0.73
1F	695.59	69	302-305	0.70
1G	702.65	67	304-307	0.65
1H	672.60	71	286-288	0.71
1J	581.49	65	248-250	0.64
1K	635.45	68	265-268	0.63

Acetyl-hydrazide was prepared from two alternative methods. In the first method, Acetyl-hydrazide was directly prepared from acid and hydrazine by using the microwave energy. Second method is conventional synthetic route of acetyl-hydrazide from amide and hydrazine, which is proved to give low yields.

Similarly, we obtained 1,2,4-triazole derivatives by using microwave technique for the synthesis of final compounds. These microwave procedures gave higher yields and were less time consuming. Fig. 7 shows the chemical scheme for the synthesis of lead compound-1a.

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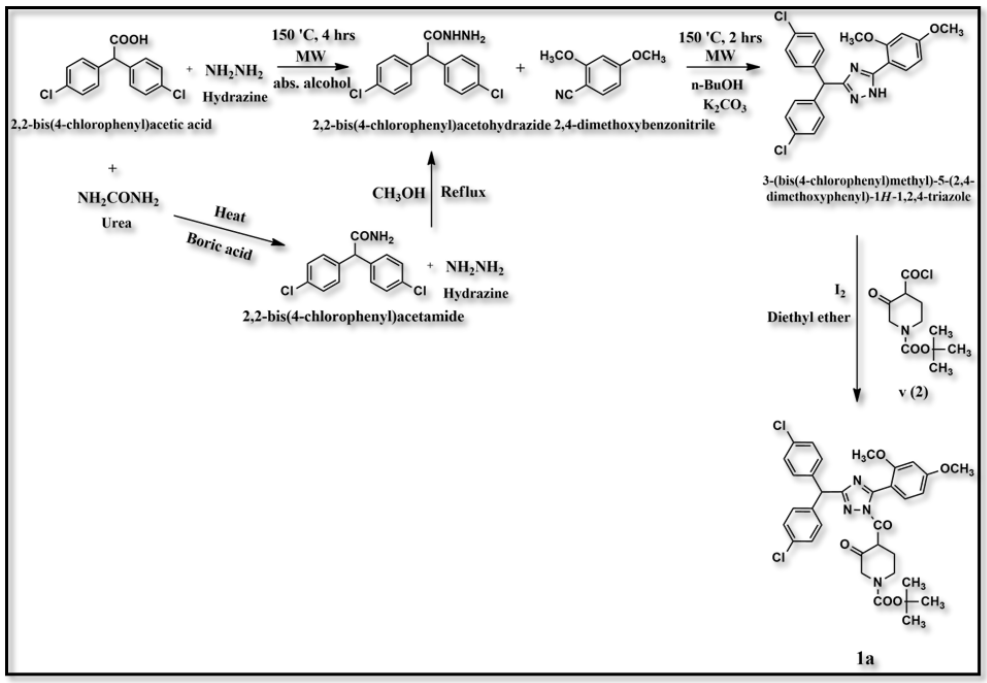

Fig. 7 *Scheme for the synthesis of lead compound 1a*

3.2 Reaction Mechanism

Formation of substituted 1,2,4-triazoles occurs by "Pellizzari Reaction". By means of microwave technique, mechanism of formation of 1,2,4-triazole is in similar manners that of Pellizzari Reaction [26]. Pellizzari Reactions is very useful for the preparation of mono, di and trisubstituted-l,2,4-triazoles. Short mechanism for the formation of disubstituted 1,2,4-triazoles from nitrile and acetohydrazide is provided in the Fig. 8.

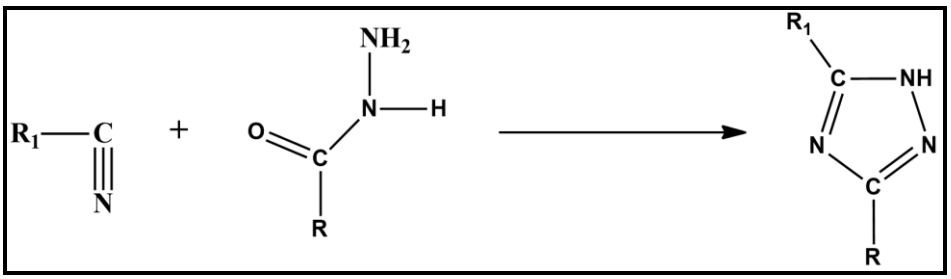

Fig. 8 *Mechanism-1 of the 1,2,4-triazoles formation*

Condensation of acetyl-hydrazide and nitrile forms the substituted 1,2,4-triazoles by using microwave method. The synthesis of 1,2,4-triazole moiety starts with construction of acetyl-hydrazide structure from the hydrazine and amide. Detail mechanism including the nucleophile attack and electron pair shifting pattern for the formation of disubstituted 1,2,4-triazoles from nitrile and acetohydrazide is provided in the Fig. 9.

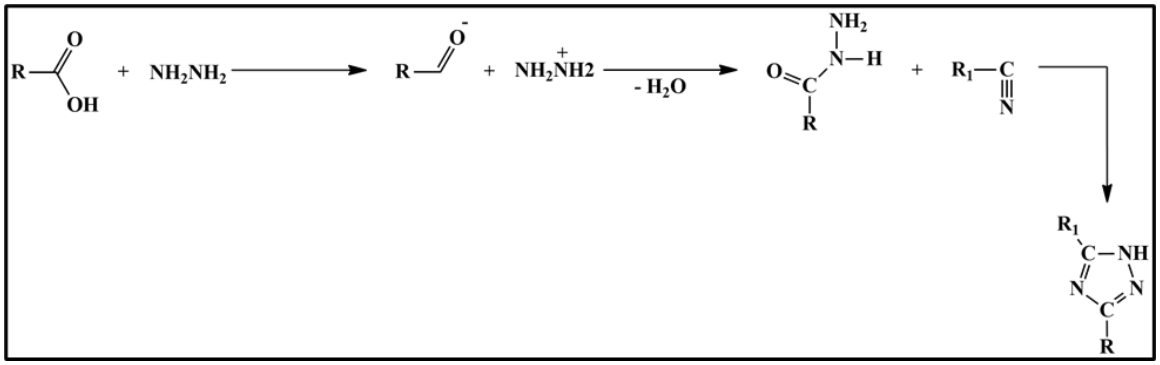

Fig. 9 *Mechanism-2 of the 1,2,4-triazoles formation [27]*

Acid and hydrazine reaction gives the acetyl-hydrazide. Reaction is initiated by activation of acid. Then activated acid is converted into a reactive oxygen species (nucleophile). And subsequent attack of the nucleophile on the hydrazine gives the final condensed product acetyl-hydrazide.

In reaction, nitrile acts as a nucleophile and attacks on the positive center of the acetyl-hydrazide. So, acetyl-hydrazide is get activated towards nucleophilic attack. Reaction follows by ring closing and condensation with the nitrile to form the final product 1,2,4-triazole.

Usually, Pellizzari reaction requires the high temperatures (more than 250°C). However, at such a high temperature, transamination may occur between reacting species and may results into a mixture of triazoles and low yield of the product [28]. But these shortcomings can be overcome by using the microwave technique for the synthesis of 1,2,4-triazole.

4. Conclusion

Many compounds with five-membered heterocyclic ring exhibit extraordinary chemical characteristics as well as diverse biological activity. For a long time, the chemistry of heterocyclic molecules has been an intriguing subject of research. Heterocyclic nucleus 1,2,4-Triazole is key class of chemicals for novel medication development. The synthesis of new 1,2,4-Triazole derivatives, as well as the examination of their chemical and biological activity, has grown in prominence in recent decades. The conventional procedures are easily replaced by this novel green chemistry based method which uses non-toxic and environmentally friendly reagents and procedure to synthesize 1,2,4-Triazole containing small molecules. The technique will undoubtedly aid in the synthesis along with environment protection

Conflict of Interest

Authors declare that there is no conflict of interests regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: ***study conception and design:*** *Chirag J. Gohil;* ***data collection:*** *Chirag J. Gohil;* ***analysis and interpretation of results:*** *Chirag J. Gohil, Malleshappa N. Noolvi;* ***draft manuscript preparation:*** *Chirag J. Gohil. All authors reviewed the results and approved the final version of the manuscript.*

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