Review Article

An overview of prior art disclosures about the synthesis of lamotrigine and a glimpse of its closely related compounds

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ABSTRACT

In this review contribution, we have gathered the specific details in brief from the prior art disclosures regarding the synthesis of **1** and its closely related compounds. The prior art disclosures were in the form of patent publications and academic journal articles. During the review process it was noticed that, most of the disclosures on the synthesis of **1** were in the form of patent publications. With an emphasis to enhance the physico-chemical properties of **1**, a few crystal/co-crystal/ionic salts of **1** are reported mainly in the academic journal articles. The glimpses of some closely related compounds to **1** are also included in this review contribution. This initiative can provide a platform for the global researchers to get an insight into the disclosures towards the synthesis of **1** and a glimpse on its closely related scaffolds. Additionally, the researchers can design new routes to commercialize **1** in future with higher atom economy by adhering to the green chemistry principles.

Key words: Lamotrigine, Cyanation, Condensation, Cyclization, Recrystallization.

Lamotrigine **1** is a popular antiepileptic drug, belongs to the class of phenyl-triazines and to the sub-class of dichloro-benzenes or halo-benzenes. It has the CAS number; 84057-84-1, Trade name; Lamictal, Molecular weight; 256.09 g/mol, Molecular formula; $C_9H_7Cl_2N_5$, and IUPAC name; 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine. It is used in the treatment of both epilepsy and as a mood stabilizer in bipolar disorder [1]. It is even prescribed for the process of conversion to drug monotherapy for those patients with at least 16 years of age or older with partial seizures and currently they are treated with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single anti-epileptic drug. Additionally, it is also used for the maintenance treatment of bipolar-I disorder in adults with at least 18 years or older, delaying the time to mood episodes (which may include mania, hypomania, depression, mixed episodes) [2].

The mode of drug actions would resemble to those of phenytoin and carbamazepine, inhibiting voltage-sensitive sodium channels, stabilizing neuronal membranes, thereby modulating the release of presynaptic excitatory neurotransmitters [3]. It exhibits the characteristic binding capability to several different receptors during the mode of its pharmacological actions [4]. It is rapidly and completely absorbed with least first-pass metabolism effects and records a reasonably high bioavailability of around 98% [5, 6]. Pharmacologically **1** undergoes routine metabolism and results in the generation of inactive metabolite 2-*N*-glucuronide conjugate. Moreover, about 94% of drug and its metabolites are eliminated through urine and around 2% would eliminate through feces [7, 8].

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OBJECTIVES

This review was focused primarily towards the exfoliation of details on the synthesis of **1** in academic journals. Additionally, salts, impurities and closely related scaffolds of **1** were also included. Interestingly, most of the synthetic routes disclosed are in the form of patent publications. In this contribution as an overview, synthesis of **1** and the glimpses of some of its closely related compounds were considered to frame the article by referring the prior publications.

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1. ***Synthesis of 1*** (*as per the disclosures in patent publications*)

Numerous patents were published in various patent trade mark offices around the globe regarding the synthesis of **1** through different synthetic pathways. Among those, majority of the synthetic pathways were reported with the use of starting material 2,3- dichlorobenzoic acid **2** to prepare **1** through the isolation of an intermediate 2,3-dichlorobenzoyl cyanide **3**. In some other illustrations, **3** was directly used as the starting material to obtain **1**. In some other examples, the penultimate intermediate of the process (2*E*,Z)-2-[cyano(2,3-dichlorophenyl)methylidene]hydrazinecarboximidamide **4** itself was cyclized under various feasible conditions to isolate **1** in high yields and good purity. In a few instances, 1,2-dichloro-3-methylbenzene **5** was used as the starting material to synthesize **1** via multi-step process. In one of the synthetic pathway, 1,2-dichloro-3-nitrobenzene **6** was employed as the starting material to isolate **1**. In addition to these synthetic procedures, a few innovative multi-step strategies were also employed to prepare **1**. To support the synthesis of **3**, a non-catalytic approach was disclosed involving halogen displacement reactions to impart an intended cyanation. The above tabulated patent disclosures (**Figure 1**) are very well elaborated with reaction schemes regarding the synthetic flourish of **1** by us in a review article [9].

Furthermore, a few catalytic approaches were also disclosed for the synthesis of **3** in good yields. Some of the close resemblance 1,2,4 triazines were reported much earlier for their synthesis and characterization [10]. A scalable process for the manufacture of **1** and other 1,2,4-triazines and their pharmaceutical applications were demonstrated by Baxter MG, *et al* [11]. A few fluoro-substituted-triazines were reported by Rees RW & Russel PB, as effective anti-malarial chemotherapeutic agents [12].

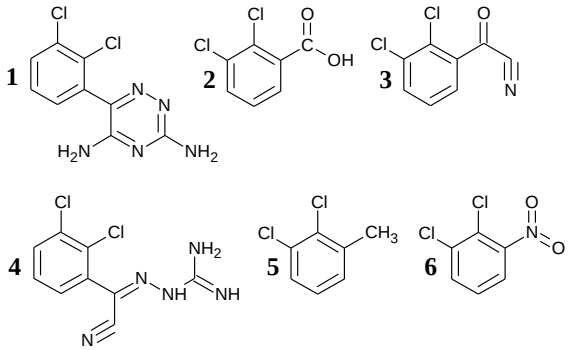


Figure 1: Product, major starting materials and intermediates featured in past patent disclosures

2. *Synthesis of **1** and a glimpse of its closely related compounds (as per the disclosures in academic journal publications)*

Hitchings GH, *et al*., had reported the use of 3,5-diamino-*as*-triazines as inhibitors of lactic acid bacteria and *Plasmodia*. Under the context, 3,4-dichlorophenyl-triazines have shown significantly superior inhibition activity against *P. berghei* [13]. Settepani JA, *et al*., had reported the condensation of acylnitriles with aminoguanidine in the presence of 2*N* nitric acid to isolate acylnitrile amidinohydrazones and its subsequent base (potassium hydroxide) mediated cyclization gave some 3,5-diamino-l,2,4-triazines [14]. This work was inspired by the past initiatives from numerous researchers towards the isolation of triazines in varied yields [15-21]. Roth B, *et al*., had attempted in vain to synthesize 3,5-diamino-6-benzyl-*as*-triazines and the reaction failure was attributed to enolization [22].

Rees RWA, *et al*., had reported the synthesis and anti-malarial activity of some chlorinated, flourinated, methoxylated, and trifluoromethylated-6-aryl-*as*-triazines **7*R***. As per the disclosure, the condensation of arylglyoxylonitriles with aminoguanidine was done under aqueous acidic medium and the intermediate amidinohydrazone salts were isolated. These salts were subjected to cyclization under simple reaction condition to isolate various triazines [23]. March LC, *et al*., had demonstrated the synthesis of many substituted 1,2,4-triazines as potential antimalarials [24]. A series of pharmacological studies of **1** was conducted by various researchers to confirm its anti-convulsant properties [25-29]. Janes RW, *et al*., had reported the crystal structure of methanol solvate of **1** [30]. Kerr DIB, *et al*., had reported the synthesis and pharmacological impact of 3-methyl-6-[2-(trifluoromethyl)phenyl][1,2,4]triazolo[4,3-*b*]pyridazine **8** [31]. Moreau S, *et al*., had demonstrated the synthesis and anti-convulsant activity of benzyl imidazo and benzyltriazolopyridazines having structural resemblance to **1** [32]. Messenheimer JA, had reported a detailed study chapter on **1** with regard to its pharmacological properties, mechanism of action, pharmacokinetic behavior etc [33].

With the solidity of clinical efficacy of **1** as an anti-convulsant drug, a few researchers including Dickins M, *et al*., had reported the synthesis of **1** in bulk for its commercialization [34]. Janes AW, *et al*., had reported the crystal growth and study of 6-(2-fluorophenyl)-1,2,4-triazine-3,5-diamine methanol solvate **9**, 6-(2-methylphenyl)-1,2,4-triazine-3,5-diamine monohydrate **10** and 6-(2-bromophenyl)-1,2,4-triazine-3,5-diamine dimethanol solvate **11** [35-37]. Sawyer DA, *et al*., had reported the synthesis and pharmacological activity of **1*I*** (isethionate salt of **1**), an important contribution in the form of patent application for the enhancement of solubility of **1** [38]. Potter B, *et al*., had reported the crystal and molecular structure of **1*I*** with an emphasis on the protonation site of *N* in the triazine ring to form an ionic salt of the drug [39].

Willmore LJ, had reported an article comprising the studies on clinical advancements and pharmacokinetics of **1** with a comprehensive prior art coverage [40]. Kubicki M, *et al*., had disclosed the hydrogen bonding patterns in **1** (hydrate)

and **1** (mesylate, hydrate) and confirmed the role of co-crystallizing solvent on the resultant hydrogen bonds [41]. Many derivatives of **1** are reported by varying the substituent atoms in the benzene ring but the triazine part was untouched. In this regard, Hlavác J, *et al*., had demonstrated the synthesis of oxo-analogues **12** and **13** of **1** and other related indole-derivatives [42]. Shridhar B, *et al*., had demonstrated the crystal structure details of benzoate-dimethylformamide solvate, dimethylformamide-sesquisolvate and hydrogen-phthalate-dimethylformamide solvate of **1** in distinct experiments [43-45]. Ulomskii EN, *et al*., had demonstrated the cleavage (using triphenylphosphine or Cu powder in acetic acid) of pre-prepared fused 6-aryl/6-hetaryl-7-aminotetrazolo[1,5-*b*][1,2,4]triazines **14*R*** in a simple accessible method to isolate a numerous 6-substituted 3,5-diamino-1,2,4-triazines. From this re-constructive disclosure, the obtained yields of isolated triazines are high and it was 76.0% for **1** [46].

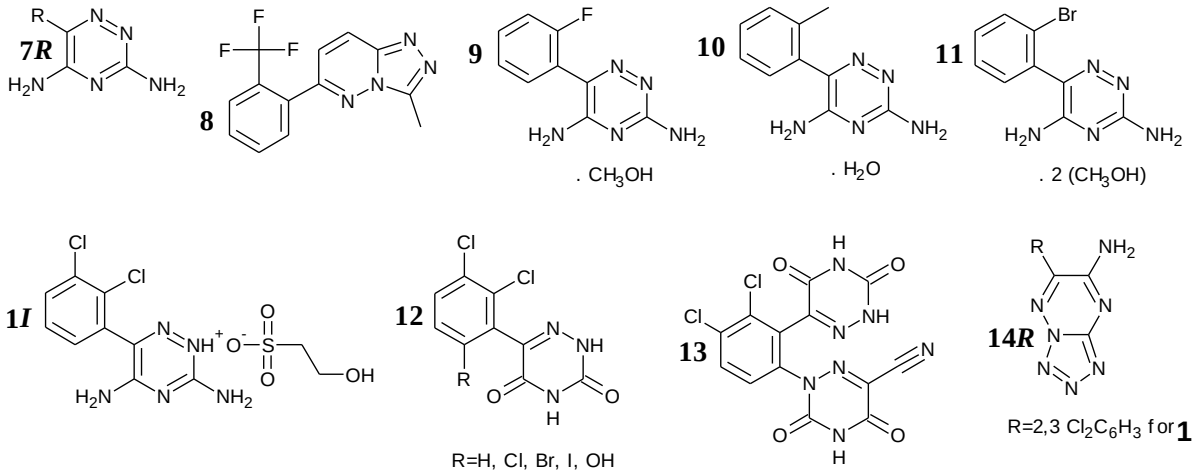


Figure 2: Major related compounds of 1 featuring in [23-46]

Reddy VV, *et al*., had reported the studies related to the synthesis, isolation and characterization of isomeric impurities of **3** (Impurity A-E) and **1** (Impurity F-J) [47]. Palmer RA, *et al*., had disclosed a report on low temperature X-ray crystallographic structures of two derivatives of **1**, 2-methyl,3-amino,5-imino-6-(2,3-dichlorophenyl)-1,2,4-triazine as water solvate **15** and 2-methyl,3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine as isethionate, hemi-hydrate **16** [48]. Palmer RA, *et al*., had reported the X-ray crystal structures of two derivatives of **1**, 3,5-diamino-6-(2-chlorophenyl)-1,2,4-triazine as hydrate **17** and 3,5-diamino-6-(3,6-dichlorophenyl)-1,2,4-triazine as methanol solvate **18** [49].

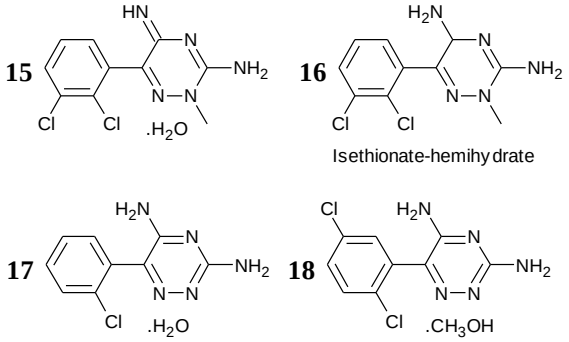
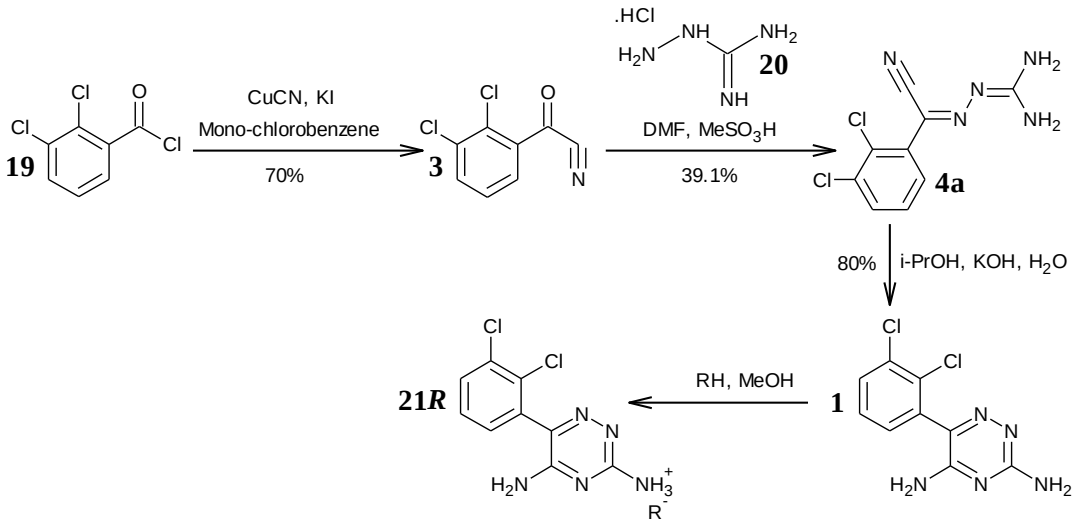


Figure 3: Related compounds of 1 featuring in [47-49]

Qian Y. *et al*., had demonstrated the synthesis, characterization and anti-microbial activity of **1** and its thirteen novel ammonium salt complexes. The work discloses an improved process for the synthesis of **1** as per ***Scheme 1***. 2,3-Dichlorobenzoyl chloride **19** was cyanated through dehalogenation using CuCN in mono-chlorobenzene to isolate **3**. The condensation of **3** with hydrazinecarboximidamide hydrochloride **20** was achieved in the presence of methanesulfonic acid ($MeSO_3H$) in DMF to obtain *N*''-[(*E*,*Z*)-cyano(2,3-dichlorophenyl)methylidene]carbonohydrazonic diamide **4a**. An alkali driven cyclization had resulted in the formation of **1**. The ammonium salts **21*R*** were prepared by treating the solution of **1** in methanol with various acids in distinct experiments. The different acids used for the salt preparation are adipic acid, propanedionic acid, chloroacetic acid, bromoacetic acid, *cis*-butenedionic acid, formic acid, fumaric acid, nitric acid, acetic acid, trifluoroacetic acid, hydrochloric acid, oxalic acid and phosphoric acid (Total: thirteen acids). As per the pharmacological studies, most of the novel salt complexes of **1** had exhibited good antibacterial activity against *Gram*-positive bacterial strains. Meanwhile, they were mild and even inactive against *Gram*-negative bacterial strains [50].

Sridhar B, *et al*., had reported the crystal studies and hydrogen bonding data of **1**, its chloride and nitrate salts [51]. Cheney ML, *et al*., had reported the studies related to the dissolution rate, solubility and pharmacokinetic behavior of ten novel forms of **1**. Those compounds are, **1** methylparaben co-crystal *form-I*, **1** methylparaben co-crystal *form-II*, **1** nicotinamide co-crystal , **1** nicotinamide co-crystal monohydrate, **1** saccharin salt, **1** adipate salt, **1** malate salt, **1** nicotinate dimethanol solvate, **1** dimethanol solvate and **1** ethanol monohydrate [52]. Razzaq SN, *et al*., had reported the

crystal structure and hydrogen bonding possibilities of novel 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazin-*2*-ium-dihydrogen-phosphate–4-(dimethylamino)-benzaldehyde **22** [53]. Sridhar B, *et al*., had reported the crystal forms of **1** with fluorobenzoic acid, nicotinic acid, 2-thiobarbituric acid, 3-picoline. Additionally, the work reports the crystal nature of butyl alcohol solvate of **1** [54]. Chadha R, *et al*., had reported the crystal structure, characterization and pharmaceutical properties of different multi-component crystalline forms of **1** with renowned coformers like nicotinamide, acetamide, acetic acid, 4-hydroxy-benzoic acid and saccharin [55]. Rao SN, *et al*., had demonstrated the synthesis, isolation, characterization and formation basis of five impurities of **1**. These reported impurities are 2-(2,3-dichlorophenyl)-2-(guanidinylimino) acetonitrile **4**, *N*-guanidinyl-2,3-dichlorobenzamide **23**, 3-amino-6-(2,3-dichlorophenyl)- 4*H*-1,2,4-triazin-5-one **24**, *N*-[5-amino-6-(2,3-dichloro-phenyl)-1,2,4-triazin-3-yl]-2,3-dichloro benzamide **25** and 3,5-*bis*-(2,3-dichloro-benzamido)-6-(2,3-dichloro-phenyl)-1,2,4-triazine **26**. Among these impurities, **23** and **26** are the novel disclosures [56].



Scheme 1 (Compound number –position to be changed, since numbers are getting cut in the view screen)

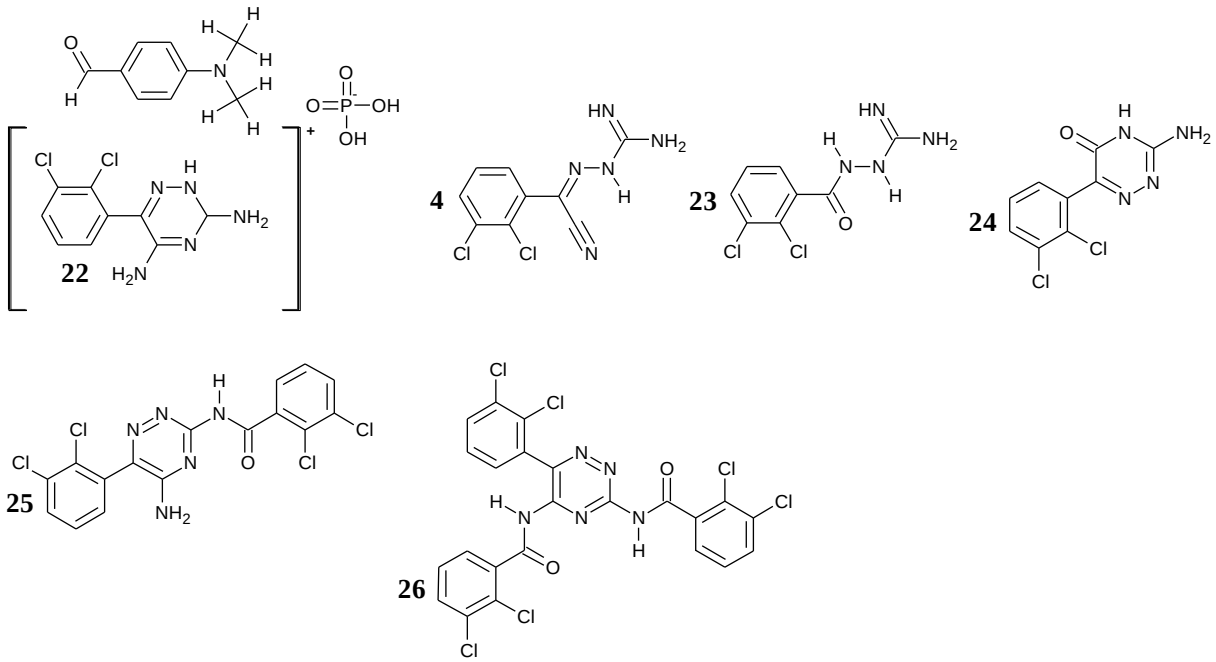
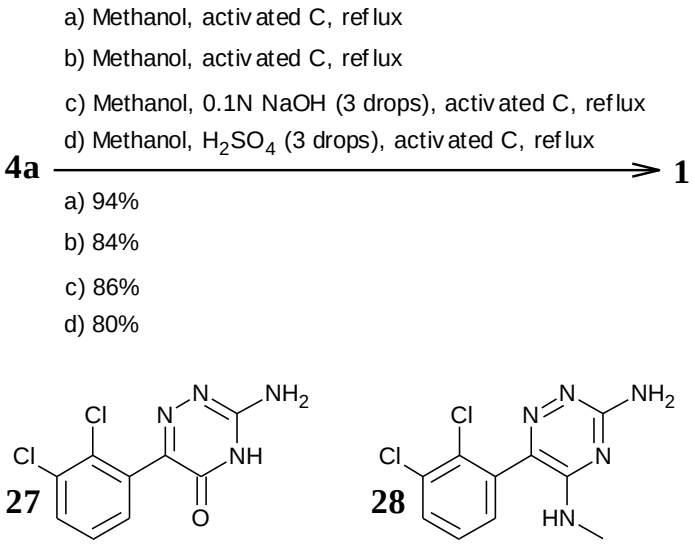


Figure 4: List of related compounds and the impurities of 1 featuring in [53-56]

Lekšić E, *et al*., had reported the synthesis, characterization and crystal nature studies of four novel co-crystals of **1** with phthalimide, pyromellitic-diimide: DMF, caffeine: 3-pentanone and isophthaldehyde [57]. With an intention to find an industrially feasible route of synthesis to manufacture **1** in high atom economy, Venkanna G, *et al*., had disclosed a high yield and an improved process than the past referred routes ***Scheme 2***. The reported work emphasizes the importance of avoiding the alkali use along with alcohol for the intended cyclization of **4a**. This adopted modification in the process will prevent the formation of 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4*H*)-one **27**, thus enhancing the process yield. Additionally, work reports the synthesis, characterization and in-process control measures about the novel 6-(2,3-dichlorophenyl)-N^5-methyl-1,2,4-triazine-3,5-diamine (*N*-methyl impurity) **28** [58].



Scheme 2: Synthesis of **1** and **28** as per Venkanna G, *et al.*

Chadha R, *et al*., had reported the crystal structure studies and the physicochemical properties of four multicomponent forms of **1** with a few carboxylic acids like acetic acid, propionic acid, sorbic acid and glutaric acid [59]. Young RB, *et al*., had disclosed a work regarding the direct photo-degradation of **1** under the impact of simulated sunlight. The rate of degradation and the by-products formed are influenced by the medium pH [60]. Leitch DC, *et al*., had demonstrated some different catalytic systems to prepare **3** from its chloride precursor. As per the conclusion of process optimization, the best cyanation (77% yield) was occurred upon the use of CuCN, cetyltrimethylammonium bromide (CTAB) in toluene [61]. Du S, *et al*., had reported the synthesis and characterization of two novel co-crystals of **1** with 4,4′-bipyridine and 2,2′-bipyridine [62]. Kaur R, *et al*., had presented the drug-drug co-crystal of two renowned anticonvulsants, **1** and phenobarbital. The work disclosed the crystal nature characterization, intrinsic dissolution rate (IDR) and solubility of the novel cocrystal [63]. Makki M, *et al*., had demonstrated the synthesis, characterization and anti-inflammatory properties of some fluorine substituted analogues of **1** [64]. Kitson PJ, *et al*., had illustrated the synthesis of **1** in a single cartridge (self-contained plastic reactionware device) through a platform-independent digital code. As per the example, 250 mg of **3** was converted **1** in a two-step process to get 112 mg of product (overall yield: 46%). This approach would pave the way for the local manufacture of drugs even in the absence of specialist facilities [65].

Matias M, had reported the synthesis and characterization of many related compounds of **1** in his thesis [66]. Kuang WJ, *et al*., had reported the synthesis, characterization and crystal nature details of two novel co-crystals of **1**. They are phthalimide co-crystal of **1** and succinimide co-crystal monohydrate of **1**. The co-crystals have enhanced solubility and dissolution rate than the pure crystalline form of **1** [67]. Kuang W, *et al*., had demonstrated the synthesis, characterization and construction of ternary phase diagrams of novel co-crystal of **1** with 1,2,3,6-4-hydro-phthalimide [68]. Heravi MM, *et al*., had contributed a review article covering the pharmacological properties, medical applications and the adopted synthetic pathways of prescribed drugs containing nitrogen heterocyclics [69]. Satapathy BS, *et al*., had illustrated the synthesis and characterization of crystalline form of **1** with citric acid. It was estimated to improve the release of **1** in gastric region and contribute to increased oral absorption [70]. Samineni R, *et al*., had illustrated the synthesis, crystal studies and physicochemical parameter estimations of co-crystals of **1** with saccharin sodium, 4-hydroxy benzoic acid, and methyl paraben. These co-crystals had exhibited better flow properties and higher dissolution rate than **1** [71]. Li J, *et al*., had reported the synthesis, crystal morphology and thermal behavior studies of two polymorphs (*form-I* & *II*) and two solvates (ethanolate & methanolate) of **1**-tolfenamic acid salt [72]. A few review articles were also published with an aim to provide a broad spectrum view on the synthetic routes, characterization and biological significance of 1,2,4-triazine derivatives but not exclusively specific to **1** [73-75].

SUMMARY

During the process to exfoliate the details of 1, we found that the disclosures on its synthesis were mainly dominated by numerous patent publications [9]. Meanwhile, academic journals had prioritized to synthesize salts and structurally close resemblance derivatives of **1**. This strategy was employed by many researchers to enhance the physico-chemical properties of 1 (Ex: solubility, stability etc) and the possible efforts to introduce the parallel drug having better clinical efficacy than 1. This review work could serve for the repurposing studies of **1** and also to venture new possibilities of synthesis.

CONCLUSION

We have retrieved the prior art details on the synthesis of **1** and its related compounds from the various web search tools/databases like Google Scholar, Google Patents, Global Dossier, Free Patents Online, USPTO Assignment, USPTO (United States Patent and Trademark Office) and Espacenet (European Patent Office and Trademark Office). This initiative is an exfoliation of **1** with regard to its synthesis by various routes. Additionally, this initiative provides the glimpses of some its very closely related compounds. This work provides an insight to the status of **1** and some of its closely related moieties in the global publications platform. In this context, this contribution is a good resource for the global researchers to plan new routes for the preparation of **1** and other associated initiatives.

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