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# Green synthesis of stroke treatment compounds: Methods and potential applications

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**ABSTRACT**

Since Stroke is a major cause of mortality and disability worldwide, safer and more efficient treatment options must be developed. By providing an environmentally friendly substitute for conventional chemical synthesis, green chemistry makes it possible to produce stroke-treating substances with a reduced negative influence on the environment. Benzimidazole derivatives, Crocetin and related oxygen diffusion-enhancing compounds, curcumin analogues, chalcone derivatives with spiro-heterocyclic and Fluorine-containing compounds are among the compounds that have shown encouraging anti-inflammatory and neuroprotective qualities. In relation to our topic, we will go over and deepen our understanding of some of the medications used to treat stroke and how they are manufactured utilizing green synthesis, which uses environmentally friendly resources and procedures, has emerged as a promising method for producing safer pharmaceuticals. Interestingly, environmentally friendly nanoparticles have shown promise in enhancing drug delivery, reducing adverse effects, and bridging the blood-brain barrier. This study discusses several green synthesis methods for compounds that have a lot of promises for treating stroke.

## Introduction

Stroke, often termed a cerebrovascular accident (CVA), happens when blood supply to a portion of the brain is blocked, causing oxygen-deficient tissue damage and nutrients[1]. It remains the second most common cause of death globally. There are several different mechanisms (connected to different risk factors) for the underlying vascular brain injury that contributes to transient ischemic attacks (TIAs) and strokes, which are clinical disorders[2]. Consequently, the diagnoses of "stroke" and "TIA" are not definitive; rather, they represent a foundation for logical research and intervention. Worldwide, stroke ranks as the



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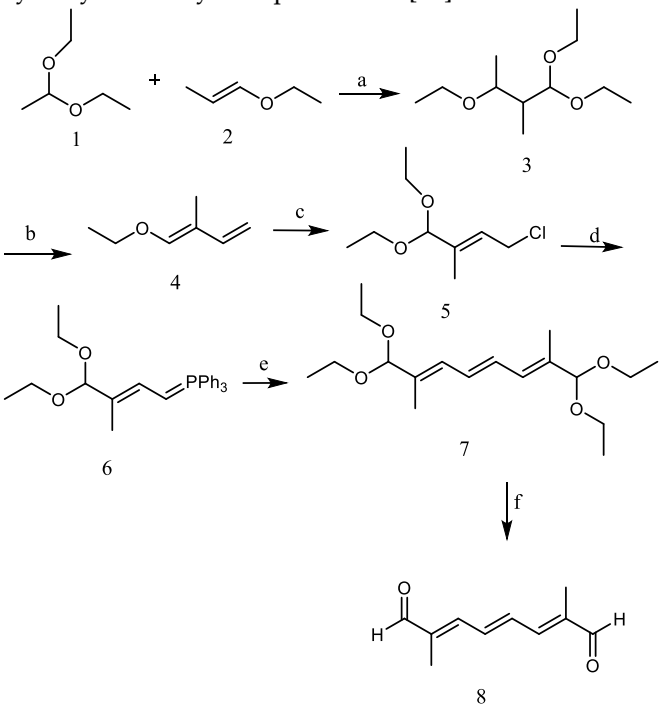
second most common cause of disability and death. Numerous risk factors, disease processes, and mechanisms can contribute to stroke; it is not a singular illness. The most significant stroke risk factor that can be changed is hypertension, even though it effects differ based on the subtype[3]. Eighty-five percent of strokes are ischemic, with People with cerebral ischemia are most classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification method [4]. Despite advances in understanding stroke pathophysiology, treatment options are limited, and traditional drug synthesis often involves hazardous chemicals[5]. Carotid stenosis, diabetes, hyperlipidemia, cigarette smoking, atrial fibrillation, hypertension, other cardiac conditions, TIA and other transient ischemic attacks are among the potentially modifiable risk factors for stroke[6]. There is ongoing research on additional possible risk factors for stroke, such as high homocysteine and alcohol, inflammation, infection, and anti-phospholipid antibodies[6]. Controlled experiments have demonstrated that reducing blood pressure can minimize the chance of stroke. antiplatelet drugs, warfarin for atrial fibrillation, lipid-lowering medications, and surgery for carotid stenosis. It is hoped that a better knowledge of stroke risk factors would lessen the burden of stroke in the future.[7] In June 1996, the Food and Drug Administration (FDA) authorized tissue plasminogen activator (t-PA) as a safe and efficient treatment for stroke provided that it is administered three hours after the stroke symptoms first appeared.. The outcomes of extensive clinical trials evaluating the effectiveness of antiplatelet antithrombotic drugs and a more prudent use of natural resources and agricultural waste followed. Both well-known chemical compounds and entirely novel materials have been produced in more ecologically friendly ways using greener techniques[8]. Numerous nanomaterials and composites can be made using greener techniques. We will review and expand on our knowledge of some of the drugs used to treat stroke, as well as how they are made using green chemistry, in connection with our topic[9]. Berberine, curcumin, quercetin, and other compounds used to treat stroke are a few examples of them[8]. Using ecologically friendly processes and resources, green synthesis has become a viable approach to creating safer medicinal substances. Notably, greenly produced nanoparticles have demonstrated the ability to improve medicine delivery, lessen side effects, and pass the blood-brain barrier[10]. Several green synthesis techniques for molecules with great potential for stroke treatment are covered in this research.

**Green Synthesis**

**1- Crocetin and associated chemicals that enhance oxygen diffusion:**

Extensive clinical research is being conducted on rans-sodium crocetinate (TSC), including COVID-19 Phase 1b/2b clinical studies. Owing to its potential to improve oxygen transport, TSC, a natural substance that is a successor to crocetin, is being researched as a radiosensitizer for a variety of malignancies[11]. TSC's special qualities make it a potentially effective treatment for a number of conditions, including heart attacks, strokes, and hemorrhagic shock[12]. Beginning with acetaldehyde diethyl acetal, (Scheme 1), followed by the condensation of compound 1 with (*E*)-1-ethoxyprop-1-ene (compound 2) producing 1,1,3-triethoxy-3-methylbutane (3) in a good yield (81–88%). Lewis acid, such as $FeCl_3$ or $AlCl_3$, catalyzed the reaction in an inert atmosphere. The following stage, (3), produced (*E*)-1-ethoxy-2-methylbuta-1,3-diene (4), under pyrolytic conditions with the help of catalysts isoquinoline and *p*TSA. Under conditions of phase-transfer catalysis (PTC: cetyltrimethylammonium bromide), a further reaction of 4 with EtOH and trichloroisocyanuric acid produced (*E*)-4-chloro-1,1-diethoxy-2-methylbut-2-ene (5). The equivalent phosphonium salt (6), which was produced by the reaction of 5 with $PPh_3$, was then reacted with $H_2O_2$ to produce the condensed intermediate 7. In a fair amount of time, the hydrolysis of 7 by acid produced 8[13].




**SCHEME 1**. Key Intermediate 8 Synthesis. Conditions and Reagents. **a.** $FeCl_3/AlCl_3$,0 to −10 °C (81% yield); **b.** isoquinoline/ pTSA 180–220 °C; **c.** i) EtOH, PTC, KOAc,



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toluene; ii) trichloroisocyanuric acid, 0–5 °C; iii) $NaHCO_3$; (75% yield); **d.** $PPh_3$, MeOH (99% yield); **e.** 0–5 °C, 35% $H_2O_2$; f. H+ (80% yield)

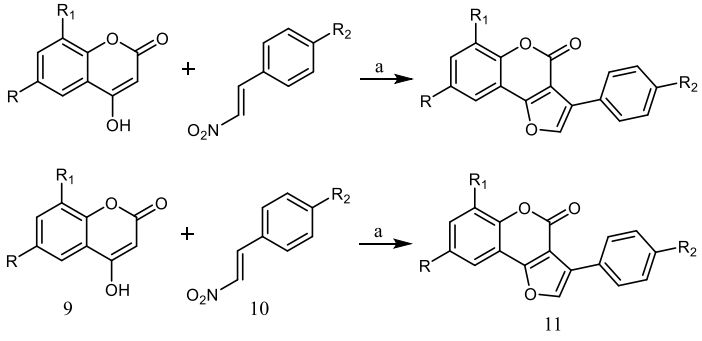
**2- Synthesis of curcumin compounds with the aid of a microwave**

Osteoporosis, Diabetes, traumatic brain injury, neurodegenerative diseases, liver damage, glioblastoma, myocardial infarction, and other different conditions can all be helped by curcuminoids[14]. Also curcuminoids have been shown to have significant anti-inflammatory and antioxidant properties[15].

Curcumin derivatives are produced when aromatic aldehydes combine with 3-acetyl-2H-chromen-2-one. Ammonium acetate and malononitrile were exposed to 350 W of microwave radiation for 6–10 minutes.

*A) Synthesis of 3-aryl-furo (11) with microwave assistance [3,2-c] coumarins*

5-milliliters of methanol containing 4-hydroxy coumarin (0.002 mol) and 2-aryl-1-nitro-ethenes (0.002 mol) After 10 minutes of stirring at room temperature, piperidine in a catalytic amount was exposed to microwave radiation for 5–7 minutes at 240 W (40%) power level[16].

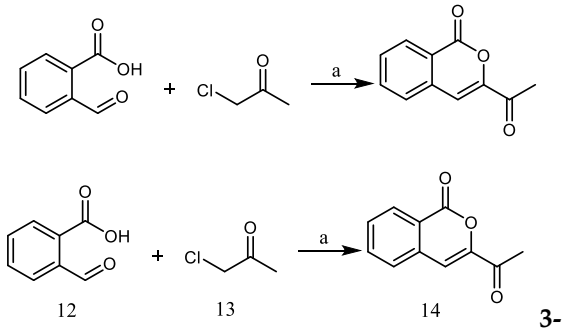



| Comp. No. | R | $R_1$ | $R_2$ | Reaction condition Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 11a | H | H | H | 5.5 | 69 |
| 11b | $CH_3$ | H | H | 6.0 | 67 |
| 11c | H | $CH_3$ | H | 5.5 | 70 |
| 11d | Cl | H | H | 5.0 | 65 |
| 11e | H | H | $CH_3$ | 5.5 | 69 |

**SCHEME 2.** Microwave-assisted 3-aryl-furo[3,2-c] coumarin synthesis. **a.** MWI,5-7 min, 240W, $CH_3OH$, Piperidine.

*B) Synthesis of isocoumarin analogues using a microwave*

A variety of therapeutic drugs are prepared using isocoumarins as synthetic precursors and intermediates. One-step synthesis of *isocoumarin* analogues with microwave assistance entails an equimolar reaction between monochloro acetone (13) and 2-formylbenzoic acid (12) with favorable yields (84–87%) for 15–30 minutes at 200 W of power while base $K_2CO_3$ is present[16].




3-

**SCHEME 3.** Microwave-assisted synthesis of isocoumarin analogs. **a.** MWI,200 W, $K_2CO_3$, 15-30 min.

3- **Benzimidazole scaffold synthesis employing an active deep eutectic solvent**

The structure and activity of bioactive compounds containing a benzimidazole nucleus vary widely[17]. Thiabendazole is the first example of a benzimidazole-based medication that is clinically available and has antiparasitic and fungicidal properties[18]. Over time, many other compounds have been developed, such as the antihistamine clemizole, the analgesic bezitramide, the anticancer bendastumide, and the anti-ulcerative Omeprazole [19].

More recently, reports have also surfaced on the effectiveness of benzimidazoles in treating conditions like hypertension and ischemia-reperfusion injury. Chemistry based on benzimidazoles has received special attention because of its characteristics and functions in several disorders. One common synthesis technique is to condense o-phenylenediamine with differently substituted aldehydes to create 2-substituted and 1,2-di-substituted benzimidazole derivatives [20]. Long reaction periods, costly reagents, using dangerous organic solvents, difficulties in the production of catalysts, the non-recoverability of the catalyst, and laborious work-up procedures are some of the disadvantages of these techniques. They describe a novel synthetic pathway to benzimidazole derivatives as part of our ongoing efforts to advance green organic chemistry. The process's unique feature is that choline chloride (ChCl) and o-phenylendiamine (o-PDA) are combined to generate a DES in the first phase[19]. Thus, we investigated DES's dual function: Reactant and solvent. The following is the final optimization of the reaction conditions: Reacting 1 mol benzaldehyde in ChCl:o–PDA (1:1) DES at 80 °C yields the monosubstituted benzimidazole derivative 17 (Scheme 4); By reacting 2 mol of benzaldehyde under the same circumstances, the 1,2-disubstituted benzimidazole 16 (Scheme 4) is produced.

This solvent system's benefit is that using the new DES offers high reaction yield, process selectivity, cost



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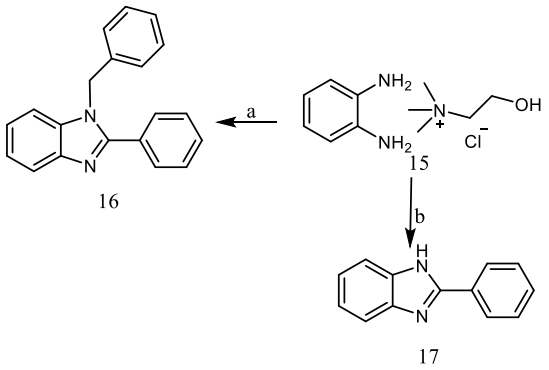
effectiveness, easy preparation of the solvent, lack of chromatographic purification and rapid reaction times [16].




**SCHEME 4.** Ideal circumstances for the pilot response. **a.** 2 mol benzaldehyde, 80$^0$c, 10 min., **b.** 1 mol benzaldehyde, 80$^0$c, 10 min., GC/MS analysis revealed that compound 17 was the sole product formed (95% yield) when using 1 mol of benzaldehyde, and the formation of compound **16** as the sole product (97% yield) when 2 moles of benzaldehyde are used.

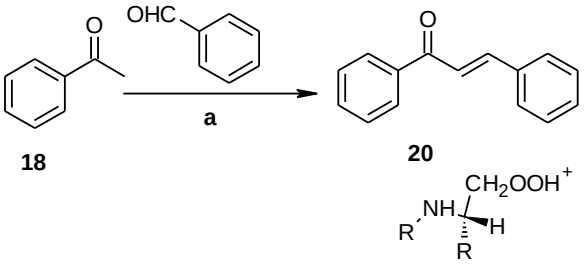
**4-Synthesis of chalcone derivatives with spiro-heterocyclic structures**

Notably, extracellular glutamate levels rise sharply after ischemic stroke, resulting in excitotoxicity in a matter of minutes and ultimately neuronal death[21]. Thus, ischemia reperfusion injury is significantly influenced by excess glutamate-induced excitotoxicity, and reducing glutamate-induced cell damage is thought to be a promising ischemic stroke therapeutic strategy. [22].

A class of molecules known as spiroheterocyclic compounds is made up of several heteroatoms and spirocyclic structures. Among these, molecules with a pyrrolidine structural unit exhibit a wide range of pharmacological actions.[16].

*Chemical synthesis*

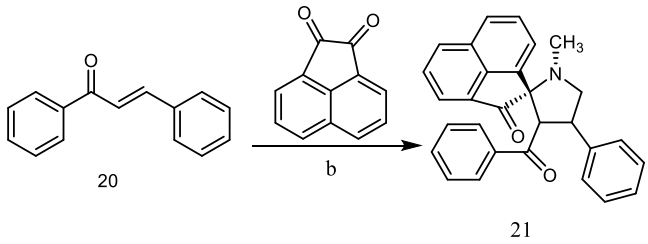
With benzaldehyde and substituted acetophenone as the raw materials, alcohol as the solvent, and sodium hydroxide or hydrochloric acid as the catalyst, chalcone $C_0$ (20) was created through a Claisen Schmidt condensation. The relevant reactants were used to create each of the intermediates connected to the chalcone. Using chalcone, amino acids, isatin, or acenaphthene quinone as raw materials, 1,3-dipolar cycloaddition was used to create spiroheterocyclic compounds. Heat reflux processes were then carried out in methanol[16].




**SCHEME 5.** Chemical synthesis. Conditions and Reagents: **a.** EtOH, 40 % NaOH. Or EtOH, HCl, quantitatively

A) Designing a low toxicity chalcone skeleton with spiroheterocyclic 21

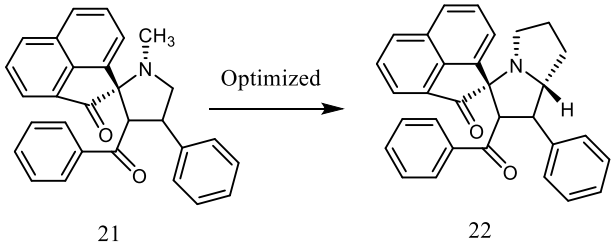
N-methyl tetrahydropyrrole was added to different spirocyclic structures, which changed the chalcone skeleton's Michael receptor. Compared to the chalcone molecular backbone C0, compound 21's cytotoxicity was noticeably lower (20).




**SCHEME 6.** Chemical synthesis. Reagents and conditions: **b.** MeOH, reflux, 3 h, 78℃, quantitative.

B) Optimizing compound **21** to obtain an active skeleton **22**

A structural unit that is biocompatible and nontoxic produced from the encoding amino acid was used to substitute the methyl group of compounds 21, producing 12 new spiroheterocyclic compounds. Only compound 22 demonstrated effective defense against damage caused by glutamate and enhanced cell survival. The predicted 22, which protects PC12 cells when glutamate is present, was obtained by optimizing 21. The lead ingredient, 21, was included in the design and synthesis of the synthetic compounds. The test chemicals (20 μ M) were applied to PC12 cells for 18 hours, followed by a 24-hour treatment with glutamate (225 mM).




**SCHEME 7.** The expected compound 22 was obtained by optimizing compound 21.

C) As a lead ingredient, compound 22 is used to produce active compound 23.



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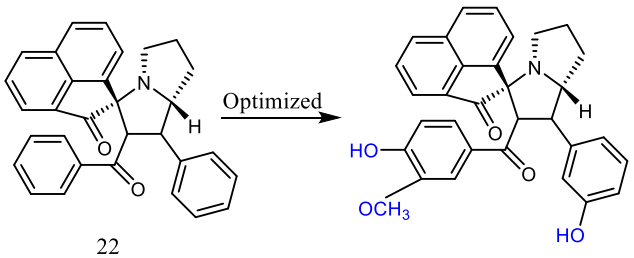
Ultimately, curcumin and other active compounds have the pharmacophore (4-OH-3-$OCH_3$), which was added to the benzene ring at both ends of **22**. As a result, some compounds with noticeably increased activity were developed. In terms of activity, by improving the seedling component **22**, the active compound **23**, which has a beneficial protective effect against glutamate-induced damage to PC12 cells, was produced. Spiroheterocyclic compound structures were designed and synthesized using **22** as the lead component. After 18 hours of incubation with the test chemicals (5 μ M), PC12 cells were treated for 24 hours with glutamate (225 mM)[16].

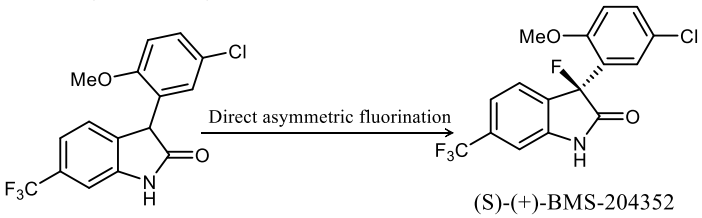



22 23

**SCHEME 8.** The active compound 23 was obtained by optimizing the seedling compound 22.

### 5- Catalytic asymmetric synthesis of MaxiPost

Synthetic chemists have been interested in molecules that include fluorine in recent decades because of their unique qualities in materials and medications. One of the most effective methods for creating chiral fluorine-containing molecules is the carbonyl compounds' enantioselective electrophilic fluorination [23]. The first effort in this area was the asymmetric fluorination of aldehydes and 1,3-dicarbonyl compounds. In terms of enhancing pharmacological efficiency, the addition of a fluorine atom to oxindoles at position three was intriguing, and N-Boc protected oxindoles eventually turned out to be suitable substrates. It was determined that the (S)-(+)-BMS-204352 (MaxiPost) was a viable treatment for stroke[24].




24 (S)-(+)-BMS-204352 25

**SCHEME 9.** Catalytic asymmetric synthesis of MaxiPost.

## Conclusion

Green synthesis marks a significant turn in the development of drugs for the treatment of stroke towards sustainable and biocompatible methods. Greenly manufactured compounds meet safety and environmental standards while also providing medicinal advantages. Green chemistry promises improved efficacy and fewer adverse effects when included into pharmaceutical research, which will advance neurovascular care.

### Ethical consideration

All the participants in this study gave their informed permission.

### Conflicts of Interest

No conflicts of interest are disclosed.

The authors reported no potential conflict of interest.

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