NRF2-Activating Compounds Bearing α,β-Unsaturated Moiety

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The surge of scientific interest in the discovery of Nuclear Factor Erythroid 2 (NFE2)-Related Factor 2 (NRF2)-activating molecules underscores the importance of NRF2 as a therapeutic target especially for oxidative stress. The chemical reactivity and biological activities of several bioactive compounds have been linked to the presence of α,β-unsaturated structural systems. The α,β-unsaturated carbonyl, sulfonyl and sulfinyl functional groups are reportedly the major α,β-unsaturated moieties involved in the activation of the NRF2 signaling pathway. The carbonyl, sulfonyl and sulfinyl groups are generally electron-withdrawing groups, and the presence of the α,β-unsaturated structure qualifies them as suitable electrophiles for Michael addition reaction with nucleophilic thiols of cysteine residues within the proximal negative regulator of NRF2, Kelch-like ECH-associated protein 1 (KEAP1). The physicochemical property such as good lipophilicity of these moieties is also an advantage because it ensures solubility and membrane permeability required for the activation of the cytosolic NRF2/KEAP1 system.

NRF2 KEAP1 α,β-unsaturated moiety

1. Introduction

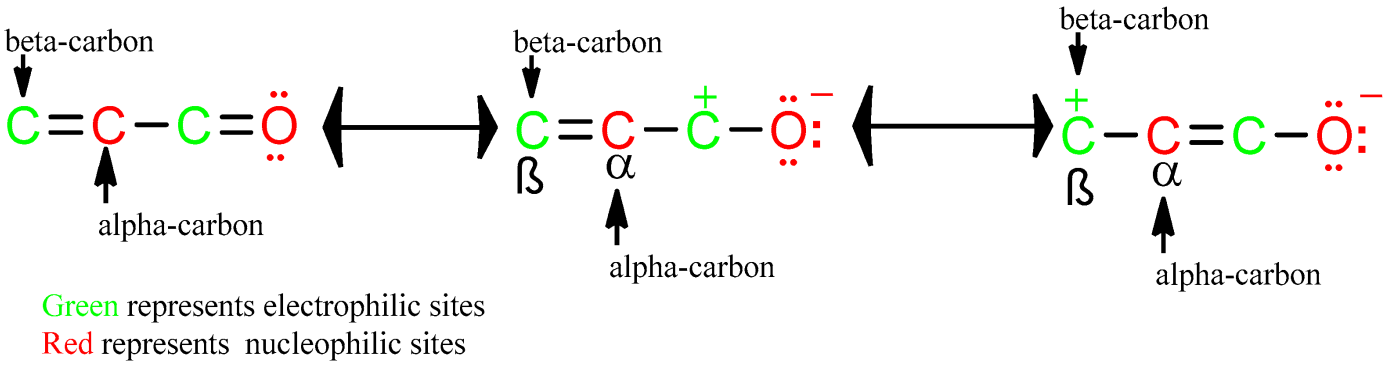
It is well established that molecules bearing α,β-unsaturated moiety constitute an essential class of electrophilic NRF2 modulators with therapeutic importance in a wide range of inflammatory and oxidative stress-mediated diseases such as Parkinson’s disease, Alzheimer’s disease, obesity, diabetes, cancer, osteoporosis, liver injury, multiple sclerosis and many others. Considering the crucial role of NRF2 in the modulation of inflammatory and oxidative processes, there is a lot of interest in the study of natural and synthetic substances capable of activating the NRF2/ KEAP1 pathway in order to design new therapeutic strategies to treat oxidative stress and inflammatory diseases. The structural peculiarity, natural abundance, facile synthetic procedures and diverse pharmacological activities of α,β-unsaturated moiety-bearing compounds including their ability to activate the NRF2/KEAP1 signaling pathway have made them important motifs of medicinal interest worthy of in-depth research. Compounds bearing α,β-unsaturated functionalities have been extensively studied [1][2][3]. Their ability to react with nucleophilic sites endows them with a multitude of biological functions including the nuclear factor erythroid 2 (NFE2)-related factor 2 (NRF2) signaling pathway activation [2][4][5][6]. Currently, NRF2, a transcription factor belonging to the cap ‘n’ collar subfamily, has become a subject of extensive research because it represents a crucial regulator of the cellular defense mechanisms against oxidative stress and xenobiotic.

Several α,β-unsaturated carbonyl, sulfonyl and sulfinyl compounds such as dimethyl fumarate (NCT00810836), curcumin (NCT01052025), chalcones and many vinyl organosulfur compounds are notable NRF2 activators [7][8][9]

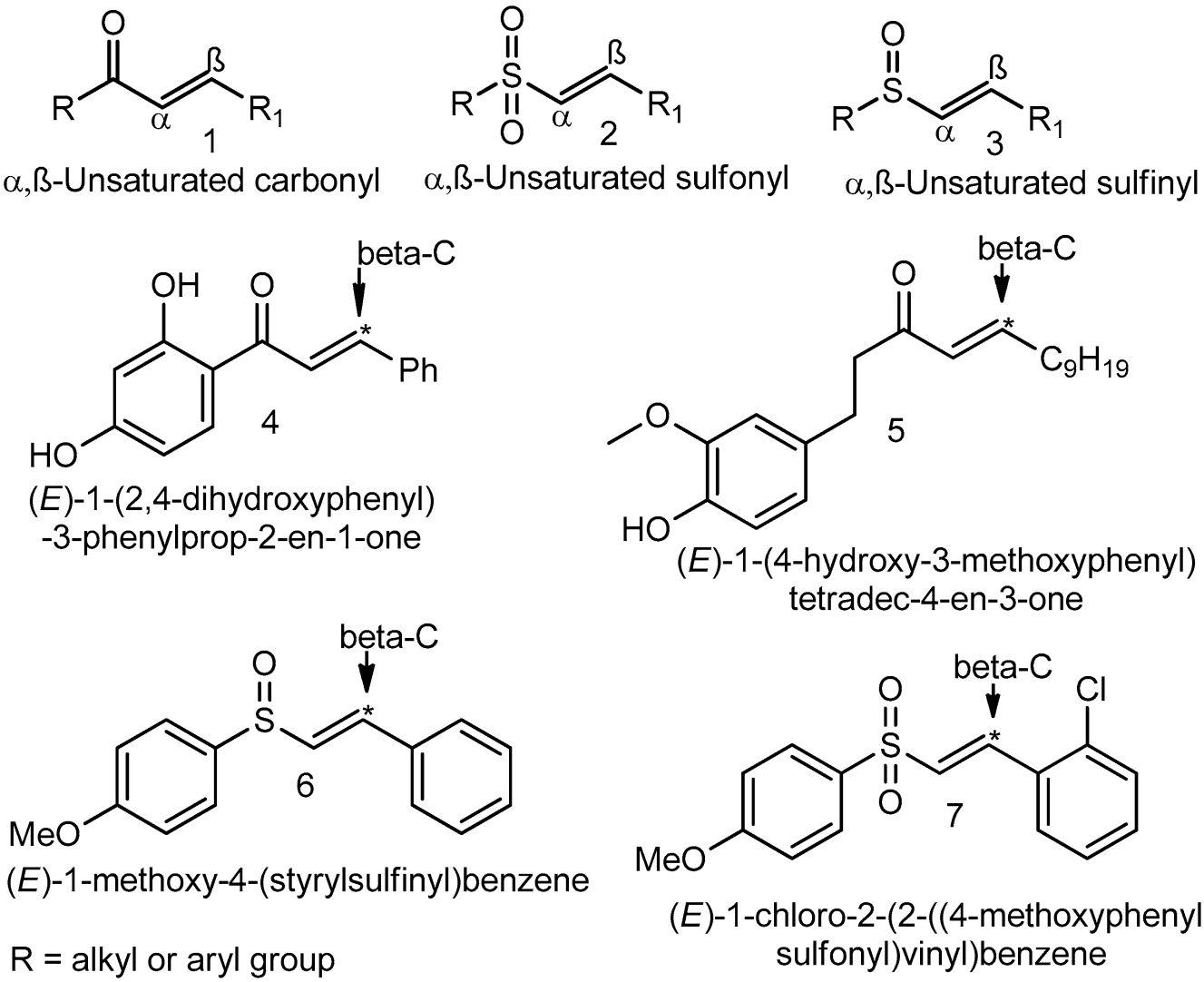
[10]. Curcumin has been evaluated in clinical trials for diseases such as impaired glucose tolerance and insulin resistance (NCT01052025). However, it has not been approved for human use due to poor bioavailability and adverse effects [11]. Chalcone derivatives such as licochalcone A have been involved in clinical trials, it has been explored for human oral squamous cell carcinoma in combination with paclitaxel (NCT03292822). Several sulfonamides have been approved by FDA as antimicrobial agents, but vinyl sulfonamides are yet to be subjected to clinical trials [12]. Amongst the sesquiterpene lactones, parthenolide, a Tanacetum derived NRF2 activator, has vast therapeutic effect in inflammation and oxidative stress-mediated diseases, especially cancer. It is in clinical trial for cancer treatment (NCT00133341). Amongst anticancer drugs currently in clinical development, parthenolide is the most promising and the first to specifically delete HDAC1 proteins without affecting other class of 1/IIHDACs in several tissue and cancer cells [13]. Despite the antioxidant and anti-inflammatory activity of helenalin an Arnica Montana-derived NRF2 activator, it is not in clinical trial and its development as an anticancer agent has been retarded probably due to allergic effects and toxicity. Costunolide exhibits significant antioxidant and anti-inflammatory effects in cancer studies [14], but no clinical trial has been conducted yet.

2. Modulation of NRF2/KEAP1 Signaling Pathway by α,β-Unsaturated Moiety-Bearing Compounds

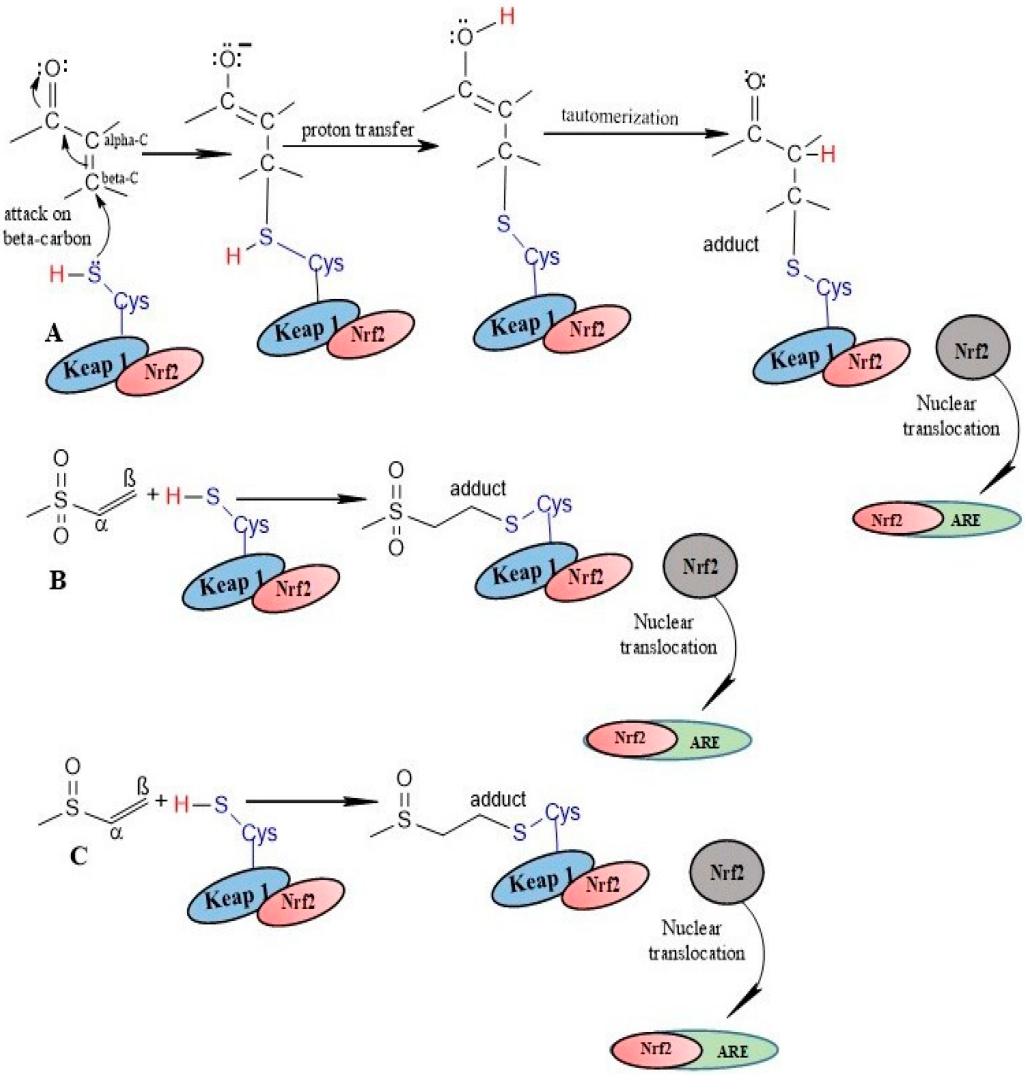
Although carbonyl and sulfonyl groups are both electron-withdrawing, the sulfonyl group tends to exhibit more of an electron-withdrawing effect than the carbonyl group. It is therefore preferred to the carbonyl group as a leaving group in nucleophilic substitution reactions [15]. However, there is a more efficient delocalization with carbonyl groups than with sulfonyl groups [15]. The beta-carbon of the α,β-unsaturated carbonyl, sulfonyl and sulfinyl groups is the most reactive electrophilic atom of these groups [16][17]. There is electron deficiency at the beta-carbon of the α,β-unsaturated carbonyl, sulfonyl and sulfinyl groups due to the electron-attracting and delocalizing activity of these moieties, and this property accounts for their electrophilicity [18][19][20]. The electrophilic character is transmitted to the beta-carbon of the double bond following the conjugation of a double bond to a carbonyl, sulfonyl and sulfinyl group in α,β-unsaturated systems. This phenomenon favors 1,4-addition reaction [21]. The resonance description of the transmission of electrophilicity to the beta-carbon (Scheme 1) [21] confirms that the beta-carbon represents the electrophilic atom at which nucleophilic thiols of cysteines are most likely to attack. Thus, the beta-carbon of α,β-unsaturated carbonyl, sulfonyl, sulfinyl groups and that of NRF2 activators containing them (**4**–**7**) are indicated in Scheme 2. The nucleophilic attack of the α,β-unsaturated structural systems by thiols of the KEAP1 cysteine residues occurs via the reaction mechanism represented in Scheme 3.



Scheme 1. A resonance description of the transmission of electrophilic character to the beta-carbon of α,β-unsaturated carbonyl system (1).



Scheme 2. A schematic view of the electrophilic beta-carbon (indicated with asterisks) of α,β-unsaturated carbonyl (1), sulfonyl (2), sulfinyl (3) and some NRF2-activating compounds containing these α,β-unsaturated moieties (4–7). The asterisks represents the point at which thiols of cysteines are most likely to attack.

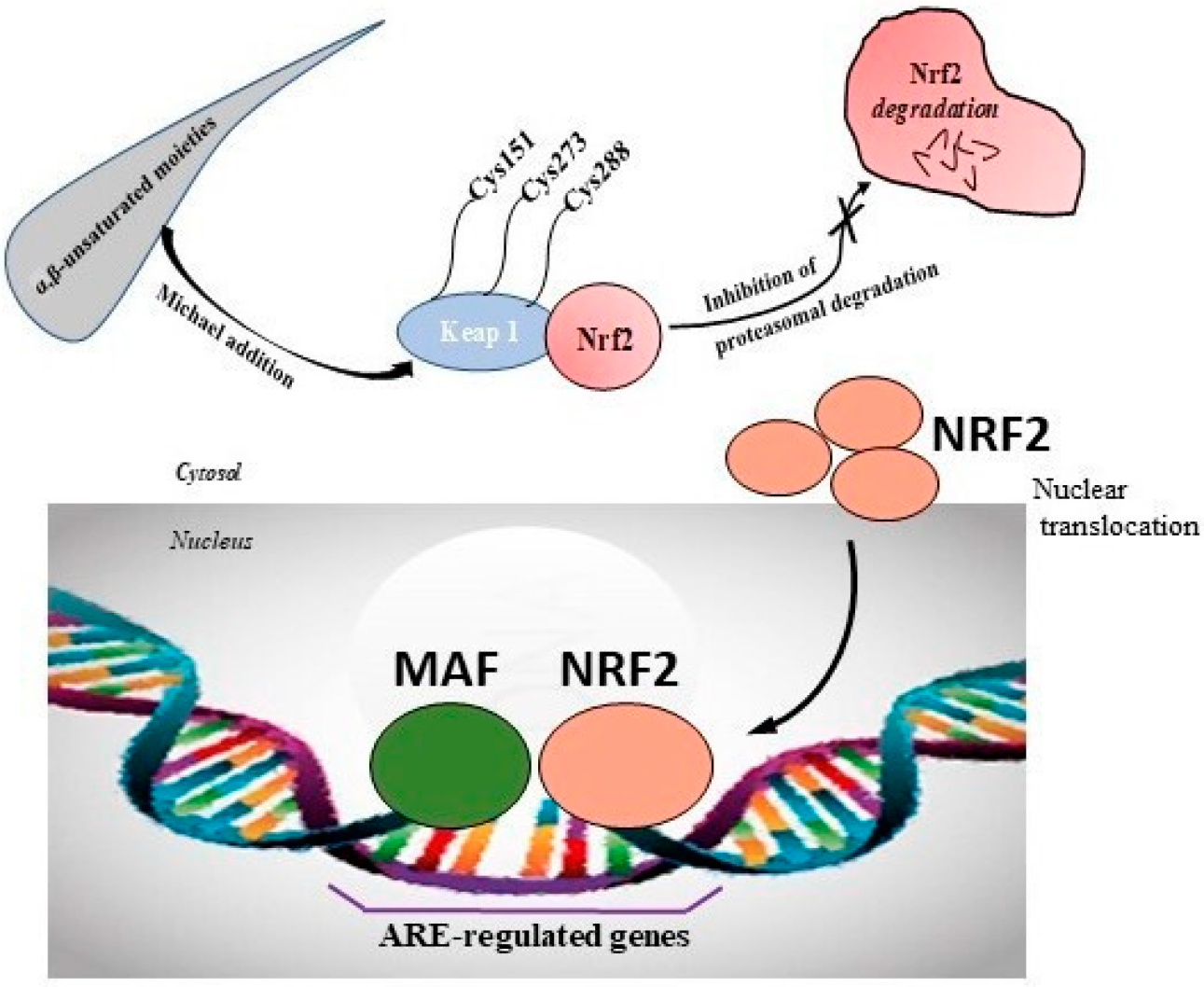


Scheme 3. Reaction mechanisms of α,β-unsaturated (**A**) carbonyl, (**B**) sulfonyl and (**C**) sulfinyl moieties. The nucleophilic attack of the thiol of the KEAP1 cysteine residues on the β carbon of the carbonyl group is followed by 1,4-addition reaction in which the thiol bonds to carbon in position 1 and hydrogen bonds to oxygen in position 4. It undergoes tautomerization to form adducts which facilitates the nuclear translocation of NRF2 (**A**). The reaction of α,β-unsaturated sulfonyl (**B**) and α,β-Unsaturated sulfinyl (**C**) with thiols of the KEAP1 cysteine residue also enable NRF2 translocation.

The electrophilic modification of the cysteine residues of cytosolic proteins by α,β-unsaturated carbonyl, sulfonyl and sulfinyl groups has been found to affect transcriptional regulation of the NRF2 signaling pathway [4][7][16]. The NRF2 pathway is likely the most sensitive pathway for electrophilic thiol-modifying molecules due to the presence of several highly reactive cysteine residues in KEAP1 [22]. Under homeostatic conditions, there is a continuous degradation of NRF2 protein in the cytoplasm by a complex of E3 ubiquitin ligase containing the regulatory cysteine-rich KEAP1 protein [23][24]. However, under oxidative stress, electrophilic α,β-unsaturated carbonyl, sulfonyl and sulfinyl compounds modify Keap1 [9][17][25]. They react with some cysteine residues of KEAP1 to form adducts that create a non-functional KEAP1 complex, thus favoring the nuclear translocation of newly translated NRF2 and facilitating transcriptional induction of NRF2–dependent genes [26][27][28][29]. Many cysteines of KEAP1

are modified by different electrophiles [26][27][30][31][32][33]. KEAP1 is a cysteine-rich protein possessing 27 and 25 cysteine residues in the human and mouse proteins, respectively. This “cysteine-code” controls KEAP1 activity. Cysteines Cys-151, Cys-273 and Cys-288 [34][35] appear to be the most susceptible to electrophilic reaction [33][36]. Based on the functional necessity of these three cysteine residues in the maintenance of KEAP1 ability to inhibit NRF2 accumulation, chemical inducers of NRF2 were categorized into four classes in relation to the cysteine on which they act [33], namely, class I (Cys151preferring), class II (Cys288 preferring), class III (Cys151/Cys273/Cys288 collaboration preferring) and class IV (Cys151/Cys273/Cys288 independent). Other sensitive cysteines are Cys-226, Cys-434 and Cys-613. Thus, considering the distinct patterns of adduct formation for each chemical inducers of NRF2, the set of optimal acceptor thiols that are functional and convert KEAP1 from the active to the inactive state should be determined.

The NRF2 activation mechanism of α,β-unsaturated moieties is represented in Scheme 4. The α,β-unsaturated sulfonyl group (**2**) acts as a 2 donor and a Michael acceptor in addition reactions [37]. The stability of the α,β-unsaturated sulfonyl and sulfinyl systems needs to be understood. The equilibrium of these functionalities can be attributed to factors such as the interaction of the α,β-double bond with the d-orbitals of sulfur in addition to the inductive effects of the sulfonyl and sulfinyl groups. In the α,β-unsaturated sulfonyl and sulfinyl systems, the double bond stabilizes by interacting with sulfur’s d-orbitals. Inductive effects on the other hand, accounts for the electron withdrawing ability of the α,β-unsaturated sulfonyl and sulfinyl groups at equilibrium in the order sulfinyl < sulfonyl. The stability of the sulfonyl group, especially sulfones, has been linked to the strength of its carbon-sulfur bond. The observed minimal role of resonance effects and the major role of inductive effects suggest that the latter is very important in the stability of these systems. The α,β-unsaturated carbonyl systems are thermodynamically more favored than α,β-unsaturated sulfonyl and sulfinyl systems, while the α,β-unsaturated sulfonyl group is more stable than the α,β-unsaturated carbonyl system [38][39][40]. Sulfonyl functional group confers dienophilic activity to the double bond attached to it [41]. The double bond in α,β-unsaturated sulfonyl-containing compounds is activated by the sulfonyl group [42]. In parallel, Choi et al. [18] reported that the α,β-unsaturated sulfonyl system is a highly active Michael acceptor for NRF2 activation. The addition of hard nucleophiles to α,β-unsaturated sulfonyl system poses some difficulties due to metalation and conjugate additions occurring as competing reactions [43]. However, the addition of soft nucleophiles, especially thiols, to the α,β-unsaturated sulfonyl group via an addition reaction is an easy and effective process [44][45].



Scheme 4. Mechanism of activation of KEAP1-NRF2-ARE pathway by α,β-unsaturated moieties. In pro-oxidant condition, the exposure to electrophilic α,β-unsaturated moieties alters the structure of NRF2/KEAP1 complex, thus inhibiting NRF2 ubiquitination and creating a non-functional KEAP1 complex. As NRF2 is not released by KEAP1, it saturates all binding sites of KEAP1, allowing newly translated NRF2 to bypass KEAP1 and translocate to the nucleus.

3. α,β-Unsaturated Carbonyls

α,β-Unsaturated carbonyl (**1**) compounds can be described as organic compounds with the general structure (O=CR)-C=C-R, in which carbonyl functional group is conjugated with an alkene [46]. For example, enones and enals exhibit vinylogues reactivity pattern which makes them prone to attack by nucleophiles at the beta-carbon [46]. In α,β-unsaturated carbonyl-based compound, one C-C bond separates the C=C and C=O bonds. The α,β-unsaturated carbonyl functionality is the most reactive substructure of synthetic and natural molecules [47][48]. The reactivity of this group explains its various pharmacological activities [48]. α,β-unsaturated carbonyls scavenge free radicals via covalent ligand binding to target proteins. They exhibit significant antioxidant and anti-inflammatory

activities by thiol trapping [48][49][50]. Data have shown that α,β-unsaturated carbonyls react with a wide range of Cys-containing amino acids, proteins and peptides [20][51]. They exhibit different molecular actions due to localization and concentration in the different targeting of certain Cysteine residues on specific proteins. Experiments performed utilizing KEAP1 mutants have demonstrated that Cys-151, Cys-273 and Cys-288 are most sensitive to electrophilic reactions with the α,β-unsaturated carbonyl group and are essential for KEAP1 to inhibit Nrf2 activity [52][53][54]. Although few α,β-unsaturated carbonyl compounds such as acrolein and its derivatives are toxic, a good number of them induce adaptive or protective responses, exhibit remarkable NRF2 activity and play important signaling functions [55][56][57][58]. Several NRF2 activators strongly depend on the presence of the α,β-unsaturated carbonyl moiety for efficacy. The α,β-unsaturated carbonyl functionality is responsible for the reactivity of several NRF2 activators, including flavones and flavonols, and when this structural feature is disrupted, the ability of these compounds to activate NRF2 is completely suppressed. Moreover, the α,β-unsaturated carbonyl group is required by polyphenols to play the role of antioxidant via NRF2 activation. Wu et al. [59] reported that α,β-unsaturated carbonyl compounds activate NRF2 pathway, and the loss of the α,β-unsaturated carbonyl moiety abrogates the NRF2 activation by these compounds. Molecules containing α-β unsaturated carbonyl groups have been shown to activate NRF2 in a reporter system and normal peripheral blood mononuclear cells [60].

3.1. Sesquiterpene Lactones

Sesquiterpene lactones are sesquiterpenoids with a lactone ring, commonly obtained from Asteraceae plant family. They are lipophilic solids that serve as a rich source of drugs because of their wide range of biological activities including antioxidant and anti-inflammatory properties [60][61][62]. Sesquiterpene lactones such as parthenolide (**8**), helenalin (**9**), alantolactone (**10**) and costunolide (**11**) have been found to significantly activate the NRF2/KEAP1 signaling pathway in different in vitro cell culture systems [63][64][65][66]. Experiments performed in rat neuronal cells demonstrated that treatment with sesquiterpene lactones promoted nuclear NRF2 translocation and ARE target genes expression, and that ARE activation was dependent on the number of α,β-unsaturated carbonyl groups present in each compound [64]. These observations strongly suggest that the bioactivities of sesquiterpene lactones, especially their ability to activate the NRF2 pathway, can be attributed to the presence of the α,β-unsaturated carbonyl unit [64][67].

3.1.1. Parthenolide

Parthenolide (**8**) is an α,β-unsaturated carbonyl-containing sesquiterpene lactone, the most abundant and active electrophilic compound obtained from feverfew plant (*Tanacetum parthenium*) [68][69]. The α,β-unsaturated lactone is reported to be the reactive part of parthenolide, not the epoxide [58]. The α,β-unsaturated carbonyl group is responsible for the electrophilic nature of parthenolide (**8**), which accounts for its ability to undergo Michael addition reaction with biochemical nucleophiles, to covalently modify proteins, and to activate the NRF2 pathway [70][71]. Kim et al. [71] reported that the antioxidant and anti-adipogenic effects of parthenolide are associated with NRF2 activation. Parthenolide (**8**) inhibits the early stage of adipogenesis, reduces the production of intracellular reactive oxygen species (ROS) and increases the expression of heme oxygenase-1 (HO-1) and NADPH dehydrogenase 1(NQO1) via the activation of the NRF2/KEAP1 signaling pathway [71]. In a similar study, Kim and co-workers [72]

attributed the anti-obese effects of parthenolide (**8**) to its ability to activate NRF2. They reported that parthenolide (**8**) suppresses adiposity-induced inflammatory responses, controls the dysregulation of adiponectin and resistin, upregulates HO-1 and promotes nuclear translocation of NRF2 in obesity and related diseases. In summary, parthenolide inhibits obesity and obesity-related inflammatory responses through the activation of the NRF2/Keap1 signaling pathway. Mao and Zhu [73] reported that parthenolide (**8**) increases the expression of NRF2, HO-1 and NQO1 in hydrogen peroxide-induced osteoblasts, thereby preventing apoptosis by the reduction in oxidative stress. Parthenolide (**8**) exhibits significant anti-tumor and anti-inflammatory activities, it inhibits inflammatory mediators and the expression of pro-inflammatory cytokines [74][75]. Additionally, the anticancer activities of parthenolide are linked to its NRF2 activity, in particular it increases the level of glutathione via the activation of the NRF2-ARE signaling pathway [76][77]. The antioxidant activity of parthenolide is dose-dependent, at low dose (<5 μM), it neutralizes hydrogen peroxide and protects against CD3-induced apoptosis in Jurkat T cells, while at high dose (10 μM) it induces oxidative stress [78]. Of note, in recent studies aimed at identifying new strategies to overcome chemoresistance and to increase the effectiveness of chemotherapy in cancer, parthenolide was found to suppress mammosphere formation and overexpression of NRF2 and its dependent genes in triple-negative breast cancer cell lines, thereby preventing resistance to doxorubicin and mitoxantrone based on ROS modulation [79][80]. It was also reported that parthenolide (**8**) activates NRF2 and it is selectively cytotoxic to chronic lymphocytic leukemia (CLL) [59].

3.1.2. Helenalin

Helenalin (**9**) is a sesquiterpene lactone obtained from Arnica montana and Arnica chamissonis foliosa containing an α,β-unsaturated carbonyl group that accounts for its anti-inflammatory, antioxidant, anti-cancer and NRF2 activities [81][82][83][84]. Lin et al. [85] reported that helenalin (**9**) inhibits oxidative stress, enhances ethanol metabolism and therefore attenuates alcohol-induced hepatic fibrosis. Li et al. [84] demonstrated that helenalin (**9**) isolated from Centipede minima (the family Asteraceae) exhibits significant antioxidant activity and anti-inflammatory effects by inhibiting NF-κB activation. It ameliorates acute hepatic injury, alleviates hepatocyte apoptosis, restores mitochondrial function and inhibits hepatic inflammatory cytokines. Helenalin (**9**) also alleviates lipid peroxidation, reduces ROS and NO production, increases antioxidant enzyme activity and HO-1 activity via activation of the NRF2 signaling pathway [84].

3.1.3. Alantolactone

Alantolactone (**10**) is a sesquiterpene lactone commonly obtained from Inula helenium *L*. It contains α,β-unsaturated carbonyl moiety. It exhibits anti-inflammatory, antioxidant, anticancer and antibacterial activities [86][87][88]. According to Liu et al. [89], alantolactone (**10**) increases the expression and nuclear translocation of NRF2. This implies that the ability of alantolactone (**10**) to promote apoptosis and suppress migration in human breast cancer cell line may depend on NRF2 signaling in addition to other pathways such as p38 and NF-κB. Soe et al. [90] reported that the induction of detoxifying enzymes by alantolactone (**10**) is mediated by NRF2. Alantolactone (**10**) enhances the activity of glutathione and increases the induction of phase II and antioxidant enzymes such as glutathione reductase, heme oxygenase-1 and γ-glutamylcysteine synthase via the NRF2-ARE signaling pathway.

It increases the nuclear translocation and activation of NRF2 in murine hepatoma (Hepa1c1c7) cells [90]. In vitro experiments conducted on human bronchial epithelial Beas-2B and NHBE cells demonstrated that alantolactone is able to prevent cigarette smoke extract (CSE)-induced pro-inflammatory cytokine production, caspase-3 activation and the increased levels of the oxidative stress markers malondialdehyde, ROS and superoxide dismutase. The same study also demonstrated that alantolactone promotes NRF2 nuclear aggregation and HO-1 expression, thus suggesting that this compound inhibits CSE-induced inflammation, apoptosis and oxidative stress by promoting NRF2 activation [91].

3.1.4. Costunolide

Costunolide (**11**) is a sesquiterpene lactone usually obtained from Inula helenium and Vladimiria souliel [92]. It has been extensively studied due to its numerous biological functions such as anti-inflammatory, antioxidant and neuroprotective activities [92][93]. Pae et al. [94] reported that costunolide (**11**) reduces inflammation by the up-regulation of HO-1 expression. Furthermore, costunolide (**11**) has been reported to improve the level of GSH in tissues and to ameliorate ethanol-induced gastric ulcer through its antioxidant anti-inflammatory activities [95][96]. Peng et al. [97] demonstrated that costunolide (**11**) prevents oxidative injuries and hinders apoptosis by promoting the nuclear translocation of NRF2, and up-regulating the expression of NRF2 downstream molecules in the neuron-like rat pheochromocytoma cell line (PC12). It upregulates antioxidant genes and reduces cellular ROS levels thus maintaining redox balance in PC12 cells. However, the knockdown of NRF2 reportedly abrogated the cytoprotective activity of costunolide (**11**), thus suggesting that its ability to promote neuroprotection is dependent on NRF2 pathway activation. In another study, costunolide (**11**) was found to induce HO-1 expression and NRF2 nuclear accumulation, to inhibit pro-inflammatory cytokines and to activate NRF2 in RAW 264.7 macrophages [94]. Similarly, Mao et al. [93] reported that costunolide (**11**) inhibits lipopolysaccharide and D-galactosamine-induced acute liver injury via NRF2 activation. It also down-regulates KEAP1 gene expression and up-regulates HO-1 and NQO1 gene expressions. Taken together, these results indicate that costunolide (**11**) exerts protective effects against acute liver injuries via its antioxidant activity by promoting the NRF2 signaling pathway.

3.2. Curcumin

Curcumin (**12**) is a phytochemical usually obtained from rhizomes of Curcuma longa that exhibits significant antioxidant and anti-inflammatory activities [98][99]. It contains an α,β-unsaturated carbonyl group that accounts for its neuroprotective effect via NRF2 activation. It has been found to promote the nuclear expression levels and biological effects of NRF2 through the interaction of the α,β-unsaturated carbonyl moiety with Cys151 in KEAP1 [100][101]. According to a recent report by Park and co-workers [102], curcumin (**12**) induces the expression of NRF2-dependent genes such as NQO1, GST-mu1 and HO-1 and increases the level of NRF2 protein in neuronal cells. The activation of NRF2 by curcumin (**12**) is reportedly accomplished via PKCα- mediated P62 phosphorylation at Ser351 [102]. Similarly, Ashrafizadeh et al. [103] reported that curcumin activates the NRF2 signaling pathway by inhibiting KEAP1, up-regulating the expression of NRF2 and its dependent genes and promoting nuclear translocation of NRF2. The pre-treatment with curcumin (**12**) prevents hemin-induced neuronal death by inducing NRF2 and antioxidant response in cultures of cerebellar neurons of rats [104]. Curcumin (**12**) also inhibits the

upregulation of inflammatory signaling-mediated KEAP1 synthesis and reduces NRF2 degradation in HepG2 cells [105]. Furthermore, curcumin (**12**) hinders oxidative stress in human nasal fibroblasts that have been exposed to urban particulate matter via the activation of the NRF2/HO-1 signaling pathway [106]. Of note, although curcumin (**12**) has been found to alleviate oxidative stress, the co-administration of curcumin and vitamin E gives a better result [107]. Co-treatment with vitamin E and curcumin of hypo- and hyper- thyroid rats resulted more efficient in down-regulating oxidative stress evaluated as lipid peroxidation and glutathione levels, and in promoting activities and protein expression of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, when compared to individual treatment. In the same study, a modeled active portion of the protein NRF2 indicated its interaction with both vitamin E and curcumin. Furthermore, in silico experiments showed the interaction of curcumin and vitamin E complex with KEAP1, suggesting that the more effective attenuation of oxidative stress by the concomitant administration of these two antioxidants might be the result of NRF2/KEAP1 pathway modulation [107].

3.3. J-Series Cyclopentenone Prostaglandin

15-Deoxy-D-prostaglandin J_2 (15d- PGJ2) (**13**) is a peroxisome proliferator-activated receptor γ ligand. It represents the J-series cyclopentenone prostaglandin and exerts cytoprotection via NRF2-mediated induction of antioxidant enzymes due to the presence of α,β-unsaturated carbonyl moiety [108][109]. Song et al. [110] corroborated the importance of the α,β-unsaturated carbonyl group in NRF2 activation by demonstrating that 9,10-dihydro-15d-PGJ2 (H_2-15d-PGJ_2), an analogue of 15d-PGJ2 that lacks α,β-unsaturated carbonyl moiety as a Michael acceptor, is not able to induce the NRF2 signaling pathway. 15d-PGJ2 (**13**) induces the up-regulation of multidrug resistance associated proteins through the activation of the NRF2-ARE signaling pathway [111]. It has been found to regulate the expression of NRF2-dependent genes and enzymes [112]. However, NADPH-dependent alkenal/one oxidoreductase reportedly attenuated the ability of 15d-PGJ2 (**13**) to affect NRF2-mediated induction of cytoprotective enzymes [111].

3.4. Chalcone and Its Derivatives

Chalcone and its derivatives exhibit significant antioxidant, anti-inflammatory and anticancer activities [113][114][115][116]. Their ability to activate the NRF2 signaling pathway has been attributed to the presence of an α,β-unsaturated carbonyl moiety [7]. Miranda-Sapla and co-workers [117] reported that *trans*-chalcone (**14**) modulates inflammatory response and enhances the total bound iron capacity via the activation of NRF2 and expression of HO-1 and ferritin. It also down-regulates ROS and NO levels in leishmania amazonensis-infected macrophages. Licochalcone A (**15**) induces nuclear translocation and activation of NRF2 through which it elevates the expression of the anti-inflammatory enzymes and determines licorice extract-induced lowered cutaneous oxidative stress in vivo [118]. Isoliquiritigen (ISL) (**16**), a natural chalcone compound, attenuates oxidative stress and inflammatory injuries via the activation of NRF2 signaling, as demonstrated in a mouse model of severe acute pancreatitis in which ISL determined a reduction in malondialdehyde, interleukin-6, tumor necrosis factor-α and cleaved-caspase-3 and an increase in NRF2, HO-1, NQO1 and superoxide dismutase (SOD) [119]. Chalcone flavokawain A (**17**) is a

chalcone derivative that suppresses lipopolysaccharide-induced inflammation through activating the NRF2/ARE-mediated genes and inhibiting the ROS/NF-κB signaling in primary splenocytes [120].

3.5. Dimethyl Fumarate

Dimethyl fumarate (DMF) (**18**) is an α,β-unsaturated carboxylic acid ester, approved for the treatment of relapsing multiple sclerosis [8][121][122]. It exhibits significant antioxidant, anti-inflammatory and NRF2 activities due to the presence of α,β-unsaturated carbonyl moiety [59][123][124]. Akin et al. [124] reported that oral administration of DMF (**18**) alleviates oxidative stress via activation of NRF2/KEAP1 pathway in mouse ovary. Gopal et al. [125] reported evidence of NRF2 pathway activation in multiple sclerosis patients that were treated with DMF in Phase 3 studies. Ahuja et al. [126] observed that DMF (**18**) activates the NRF2 pathway, depletes glutathione level, decreases the viability of cells and inhibits mitochondrial oxygen consumption in a dose-dependent manner. Based on these observations, they recommended the development of monomethyl fumarate (MMF) a bioactive metabolite of DMF, which does not exhibit similar adverse effects, as a novel Parkinson's disease drug [126]. In summary, the reactivity of α,β-unsaturated carbonyl system with thiols of the KEAPl cysteine residues is responsible for the activation of the NRF2 signaling pathway and accounts for the antioxidant and anti-inflammatory activities of α,β-unsaturated carbonyl-containing compounds. DMF is a notable multi-target compound that modulates NRF2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), hydrocarboxylic acid receptor (HCAR2) pathways and regulates glutathione and iron metabolism which is utilized for the treatment of neurodegenerative diseases [127].

4. α,β-Unsaturated Sulfonyls

The sulfonyl group is an electron-withdrawing moiety found in several organosulfur compounds such as sulfones, sulfonamides and sulfonates [15][128]. The strong electron-withdrawing effect of the sulfonyl group accounts for the tendency of α,β-unsaturated sulfonyls to add to nucleophiles in order to form Michael-type adducts. This property also makes α,β-unsaturated sulfonyls to act as powerful dienophiles [129]. Several sulfonyl-containing compounds exhibit significant antioxidant and anti-inflammatory activities [130][131][132][133]. α,β-unsaturated sulfonyls are notable building blocks in the synthesis of organic compounds [134]. They exhibit notable biomedical significance [135]. They inhibit several enzymatic processes making them essential moieties in drug design and medicinal chemistry [37]. The first α,β-unsaturated sulfonyls were reported as potent inhibitors of cysteine proteases in 1995 [136]. They are inhibitors of cruzain, HIV-1 integrase, *Staphylococcus* aureus sortase, among others [137][138][139]. α,β-unsaturated sulfonyls reversibly inhibit diverse enzymes via conjugate addition reaction with the thiols of cysteine residue [136][139][140]. They are effective for intracellular inhibition of dipeptidyl peptidase1 [141][142]. α,β-unsaturated sulfonyls are reportedly activators of the NRF2 signaling pathway [2][9][16][143].

4.1. Vinyl Sulfones

Vinyl sulfones have been reported as modulators of NRF2 activity due to the presence of the α,β-unsaturated sulfonyl system that accounts for their effectiveness as Michael acceptors [2][9][18]. Carlstrom et al. [2] reported that vinyl sulfone (**19**) activates the NRF2 signaling pathway with limited off-target effects on hypoxia-inducible factor 1

and NF-κB in PTRAF-transfected HEK293 cells. Lee and co-workers [16] also reported that compound **19** activates NRF2 signaling and induces the up-regulation of the expression of NRF2-dependent antioxidant enzymes in microglia. It inhibits the expression of proinflammatory enzymes and proinflammatory cytokines production in activated microglia. Woo et al. [143] reported that compound **19** in dopaminergic (DAergic) neuronal cells activates NRF2 and up-regulates the expression of NRF2-regulated antioxidant enzymes at mRNA and protein levels. It exerts neuroprotection and attenuates Parkinson's disease (PD)-related deficits in PD mouse models [144]. Choi and co-workers [9][18] corroborated that compound **19** activates NRF2 and induces the expression of NRF2-regulated antioxidant mediators in PD mice. Although extensive researches have proven that compound **19** exhibits the highest NRF2 activity amongst its vinyl sulfone analogues, however, its poor drug-like properties remain a concern. In view of this, Choi et al. [18] designed a vinyl sulfone derivative (**20**) with improved NRF2 activation potency and drug-likeness. Compound **20** significantly induces NRF2 activation, up-regulation of NRF2-dependent genes, improves the movement ability in acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD mice and reduces microglial activation and loss of DAergic neurons [18]. Vinyl sulfone derivative (**21**) is reportedly more potent than chalcone and vinyl sulfoxide analogues in activating the NRF2 signaling pathway and up-regulating the expression of HO-1 gene [143]. Vinyl sulfone compounds **22** and **23** induce the relief of H_2O_2-induced lesions, neutralize ROS, activate antioxidant response and promote neuroprotection via the activation of NRF2 pathway in PC12 cells. However, the neuroprotective activity of compound **22** is higher than that of compound **23** [145]. The electrophilicity and steric hindrance of α,β-unsaturated sulfones have been tuned to generate several potent NRF2 activators [145].

4.2. Vinyl Sulfonamides

Sulfonamides exhibit antioxidant and anti-inflammatory activities [146][147][148][149][150][151][152]. The presence of the α,β-unsaturated sulfonyl system in vinyl sulfonamides enable them to act as Michael acceptors and activate the NRF2 signaling pathway [18]. Choi and co-workers [18] synthesized several vinyl sulfonamides by substituting the sulfone moiety of compound **19** with sulfonamide moiety to improve NRF2 activation ability. The analysis of antioxidant enzymes and inflammatory cytokines expression in BV-2 microglial cells and SH-SY5Y human neuroblastoma cells, and of in vivo therapeutic effects on Parkinsonism in a mouse model of Parkinson's disease showed that compounds **24**, **25**, **26**, **27**, **28** exhibit NRF2 activity and compound **26** is the most potent NRF2 activator. However, compound **26** is not as potent as the vinyl sulfonate analogues [18].

4.3. Vinyl Sulfonates

Sulfonates exhibit antioxidant and anti-inflammatory activities [153][154]. Vinyl sulfonate are highly activated Michael acceptors due to the α,β-unsaturated sulfonyl moiety they contain [18]. Vinyl sulfonate compounds **29**, **30** and **31** have been reported as potent activators of the NRF2 signaling pathway [18]. They exert therapeutic effects against Parkinson's disease via their antioxidant, anti-inflammatory and neuroprotective activities [18]. Compound **29** exhibits about seven times NRF2 activity higher than its vinyl sulfone analogue (**19**). Compound **29** increases NRF2-related protein levels attenuates inflammation and decreases the production of NO in BV-2 cells. It also up-

regulates the expression of NRF2-regulated antioxidant enzymes and inhibits motor deficits in Parkinson's disease [18].

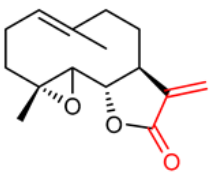
5. α,β-Unsaturated Sulfinyls

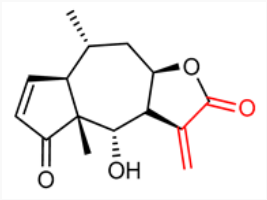
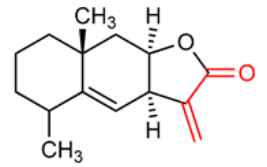
The sulfinyl group is available in several organosulfur compounds. It is a strong electron-withdrawing moiety and exhibits high configurational stability and several biological functions such as antioxidant, anti-inflammatory and NRF2 up-regulation activities [155][156][157][158]. Recently, sulfinyl group has been utilized in controlling the enantioselectivity of 1,4-additions involving carbon nucleophiles to α,β-unsaturated sulfoxides [159]. Similarly, α,β-unsaturated sulfinyl group is a very essential partner in Michael addition reaction involving thiols of the KEAP1 cysteine residues in NRF2 activation [160][161]. α,β-unsaturated sulfinyl compounds activate the NRF2 signaling pathway.

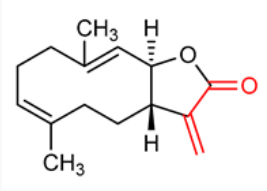
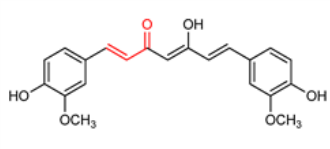
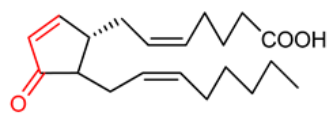
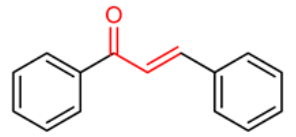
Vinyl Sulfoxide

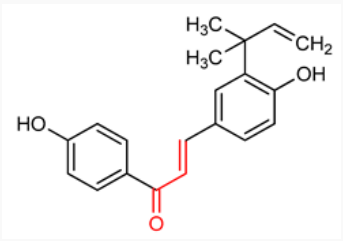
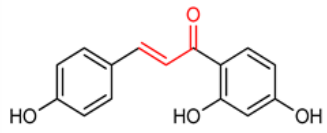
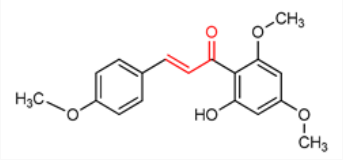
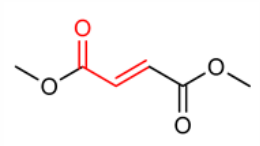
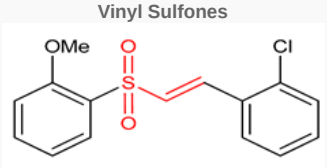
Sulfoxides exhibit antioxidant and anti-inflammatory activities [160][162]. The ability of vinyl sulfoxide to activate NRF2 and to induce HO-1 has been linked to the presence of an α,β-unsaturated sulfinyl system [143]. Woo and co-workers [143] synthesized vinyl sulfoxide (**32**) based on chalcone structure. In an attempt to determine the NRF2-activating potency of compound **32.** Woo et al. [143] assessed its ability to induce the expression of a NRF2-dependent genes in BV2 cells. Compound **32** was found to exhibit significant HO-1 inducing activity and confirmed to be a potent as its vinyl sulfone and chalcone analogues [143]. Shim et al. [3] designed and synthesized vinyl sulfoxide derivatives (**33** and **34**) using sulforaphane and gallic acid as structural templates and tested their HO-1 inducing ability as the measure of NRF2 activation in BV2 microglial cells. However, compounds **33** and **34** exhibit moderate HO-1 inducing activity and no inhibitory effect on NO production [3], thus suggesting that a more efficient electrophile is needed to get more effective NRF2 activator. α,β-unsaturated sulfinyl compounds activate the NRF2 signaling pathway as shown in **Table 1**.

Table 1. α,β-Unsaturated moiety-bearing compounds as NRF2 activators/KEAP1 inhibitors.

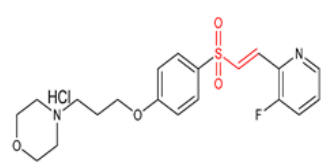
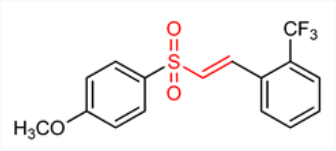
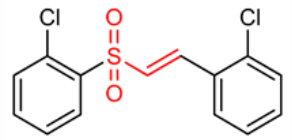
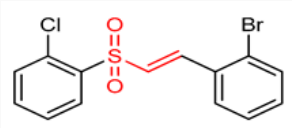
S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
8	**Sesquiterpene lactones**  Parthenolide	Obesity	Mice, Adipocytes (3T3-L1), RAW264.7	1–8 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-adipogenesis	[124]
		Obesity	3T3-L1 Cell	1–8 μM		NRF2 activation, Antioxidant, Anti-inflammatory	[125]

S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
		Osteoporosis	Human	5–20 μM		NRF2 activation, Antioxidant, Anti-apoptosis	[126]
		Breast cancer	Human breast cancer cell line MDA-MB 231	2.0 μM		NRF2 regulation, chemoresistance	[133]
		Chronic lymphocytic leukemia	Human peripheral blood mononuclear cells (PBMCs)	1.46 μM		NRF2 activation, Antioxidant, cytotoxicity	[111]
9	 Helenalin	Acute hepatic injury	Male C57BL/6 Mice	0.75–3.00 mg/kg	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[137]
10	 Alantolactone	Breast cancer	MCF-7 human breast cancer cells	10–30 μM		NRF2 activation, anticancer	[142]
		Cancer	Heps1c1c7 cells	1–10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, anticancer	[143]
		Chronic obstructive pulmonary disease (COPD)	Cigarette smoke-induced human bronchial epithelial cells	1–10 μM		NRF2 activation, Antioxidant, Anti-inflammatory	[144]

S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
11	 Costunolide	Acute liver injury	Mice	20–40 mg/kg	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[146]
		Oxidative damage	PC12 Cells	5 µM		NRF2 activation, Antioxidant, neuroprotection	[150]
		Tumor	RAW264.7 Macrophages	0.1–1.0 µM		NRF2 activation, Anti-inflammatory	[147]
12	**Curcumin** 	Neurodegenerative diseases	Neuronal cells	10 µM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant	[155]
		Oxidative stress, inflammation	HepG2 Cells	50 mg/kg		NRF2 activation, Antioxidant, Anti-inflammatory	[158]
		Nasal diseases	Human nasal fibroblast	0–5 µM		NRF2 activation, Antioxidant	[159]
		Oxidative stress	Rats	30 mg/kg		NRF2 activation, Antioxidant	[160]
13	**Prostaglandin**  15-Deoxy-$\Delta^{12,14}$-prostaglandin J2	Breast cancer	Human breast cancer cells	10 µmol/L	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant	[163]
		Cancer	Mouse embryonic fibroblast (MEF) 293 cells	0.5–10 µM		NRF2 activation, Antioxidant, Anticancer	[164]
14	**Chalcones**  *Trans*-chalcone	Leishmannia amazonensis	L. amazonensis-infected macrophages	2–12 µM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant,	[169]

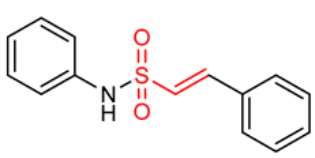
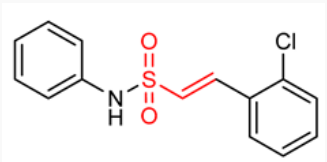
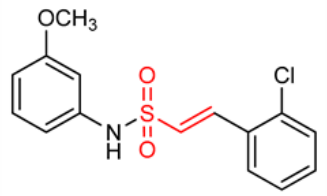
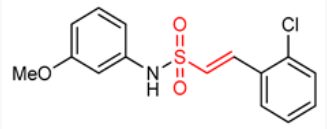
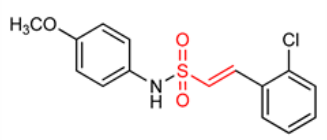
S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
15	 Licochalcone A	Cutaneous oxidative stress	UVA-irradiated human dermal fibroblast	9 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[170]
16	 Isoliquiritigenin	Pancreatic injury	Mice	>3%	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[171]
17	 Chalcone flavokawain A	inflammation	Primary splenocytes	2–30 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[172]
18	DMF  Dimethyl fumarate	Oxidative stress	Mouse ovary	20 mg/kg	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant,	[175]
		Multiple sclerosis	Multiple sclerosis patient	0–400		NRF2 activation, Antioxidant,	[173]
		Parkinson's disease	Mice	0.05–80 μM		NRF2 activation, Antioxidant, Anti-inflammatory	[177]
19	Vinyl Sulfones  (E)-1-chloro-2-(2-((2-methoxyphenyl)sulfonyl)vinyl)benzene	Multiple sclerosis	HEK293	10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant,	[2]
		Parkinson's disease	PD animal model	1–20 μM		NRF2 activation, Antioxidant, Anti-inflammatory	[23]

1. Sulsen, V.P.; Martino, V.S. Sesquiterpene Lactones: Advances in Their Chemistry and Biological Aspects, 1st ed.; Springer Nature: Cham, Switzerland, 2018.
2. Carlstrom, K.E.; Chinthkindi, P.K.; Espinosa, B.; Nimer, F.A.; Arner, E.S.J.; Arvidsson, P.I.; Piehl, F.; Johnasson, K. Characterization of more selective central nervous system NRF2-activating novel vinyl sulfoxime compounds compared to dimethyl fumarate. Neurotherapeutics 2020, 17, 114–1152.
3. Shim, S.Y.; Hwang, H.S.; Nam, G.; Choi, K. Synthesis and NRF2 activating ability of thiourea and vinyl sulfoxide derivatives. Bull. Korean Chem. Soc. 2013, 34, 2317–2320.
4. Mayer, R.J.; Allihn, P.W.A.; Hampel, N.; Mayer, P.; Sieber, S.A.; Ofial, A.R. Electrophilic reactivities of cyclic enones and α,β-unsaturated lactones. Chem. Sci. 2021, 12, 4850–4865.

S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
	unsaturated sulfonyl compou	Parkinson's disease	PD animal model	1–10 μM	553.	NRF2 activation, Antioxidant, Neuroprotection	[32]
20	 (E)-4-(3-(4-((2-(3-fluoropyridin-2-yl)vinyl)sulfonyl)phenoxy)propyl)morpholine hydrochloride	Parkinson's disease	PD mice	0.3–10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Neuroprotection	[9]
21	 (E)-1-(2-((4-methoxyphenyl)sulfonyl)vinyl)2-(trifluoromethyl)benzene	Parkinson's disease	PD mice	20 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Neuroprotection	[32]
22	 (E)-1-chloro-2-(2-((2-chlorophenyl)sulfonyl)vinyl)benzene	Oxidative stress	PC12 Cells	2.5–1.0 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Neuroprotection	[194]
23	 (E)-1-bromo-2-(2-((2-chlorophenyl)sulfonyl)vinyl)benzene	Oxidative stress	PC12 Cells	0.5–1.0 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Neuroprotection	[194]

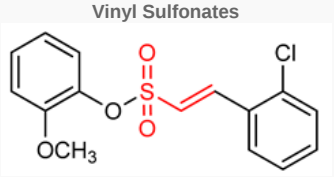
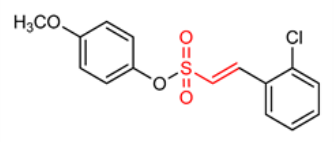
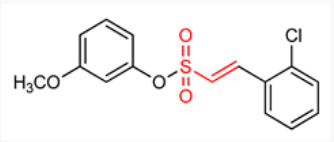
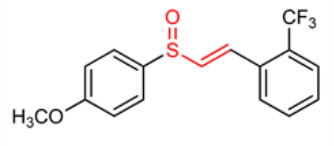
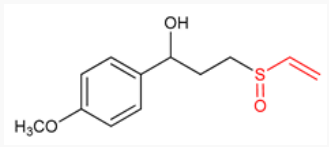
significance of sulfur (SVI)-containing motifs for drug discovery: A critical review. Eur. J. Med. Chem. 2019, 162, 679–734.

13. Lu, L.; Feng, Q.; Su, T.; Cheng, Y.; Huang, Z.; Huang, Q.; Liu, Z. Chapter 35, Pharmacoepigenetics of Chinese herbal components in cancer. In Translational Epigenetics, Pharmacoepigenetics; Cacabelos, R., Ed.; Academic Press: Cambridge, MA, USA, 2019; Volume 10, pp. 859–869.
14. Rasul, A.; Parveen, S.; Ma, T. Costunolide: A novel anticancer sesquiterpene lactone. Bangladish J. Pharmacol. 2012, 7, 6–13.
15. Chataigner, I.; Panel, C.; Gerard, H.; Piettre, S.R. Sulfonyl Vs. Carbonyl group: Which is the more electron–withdrawing? Chem. Commun. 2007, 31, 3288–3290.
16. Lee, J.A.; Kim, J.H.; Woo, S.Y.; Son, H.Y.; Han, S.H.; Jang, B.K.; Choi, J.W.; Kim, D.J.; Park, K.D.; Hwang, O. A novel compound VSC2 has anti-inflammatory and antioxidant properties in microglia and in Parkinson's disease model. Br. J. Pharmacol. 2015, 172, 1087–1100.

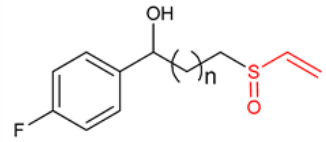
S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
	Vinyl Sulfonamides						
24	 (E)-N,2-diphenylethenesulfonamide	Parkinson's disease	PD mouse	>10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
25	 (E)-2-(2-chlorophenyl)-*N*-phenylethesulfonamide	Parkinson's disease	PD mouse	>10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
26	 (E)-2-(2-chlorophenyl)-N-(2-methoxyphenyl)ethenesulfonamide	Parkinson's disease	PD mouse	6.35 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
27	 (E)-2-(2-chlorophenyl)-N-(3-methoxyphenyl)ethane sulfonamide	Parkinson's disease	PD mouse	>10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
28	 (E)-2-(2-chlorophenyl)-N-(4-	Parkinson's disease	PD mouse	>10 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]

cysteines of the electrophile sensing human Keap1 protein is insufficient to disrupt binding to the Nrf2 domain Neh2. Proc. Natl. Acad. Sci. USA 2005, 102, 10070–10075.

26. Cuadrado, A.; Manda, G.; Hassan, A.; Alcaraz, M.J.; Barbas, C.; Daiber, A.; Ghezzi, P.; Leon, R.; Lopez, M.G.; Oliva, B.; et al. Transcription factor NRF2 as a therapeutic target for chronic diseases: A system medicine approach. Pharmacol. Rev. 2018, 70, 348–383.
27. Cuadrado, A.; Rojo, A.I.; Wells, G.; Hayes, J.D.; Cousin, S.P.; Rumsey, W.L.; Attucks, O.C.; Franklin, S.; Levonen, A.L.; Kensler, T.W.; et al. Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases. Nat. Rev. Drug Discov. 2019, 18, 295–317.
28. Taguchi, K.; Motohashi, H.; Yamamoto, M. Molecular mechanisms of the KEAP1–NRF2 pathway in stress response and cancer evolution. Genes Cells 2011, 16, 123–140.

S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
	methoxyphenyl)ethane sulfonamide						
	Vinyl Sulfonates						
29	 (E)-2-methoxyphenyl 2-(2-chlorophenyl)ethenesulfonate	Parkinson's disease	PD mouse	0.076 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
30	 (E)-4-methoxyphenyl 2-(2-chlorophenyl)ethenesulfonate	Parkinson's disease	PD animal model	0.237 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
31	 (E)-3-methoxyphenyl 2-(2-chlorophenyl)ethenesulfonate	Parkinson's disease	PD mouse	0.165 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant, Anti-inflammatory	[17]
	Vinyl Sulfoxides						
32	 (E)-1-(2-((4-methoxyphenyl)sulfinyl)vinyl)-2-(trifluoromethyl)benzene	Parkinson's disease	BV-2 Cells	20 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Neuroprotection	[32]
33	 1-(4-methoxyphenyl)-3-	Parkinson's disease	BV-2 Cells	20 μM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant,	[3]

38. O'Connor, D.E.; Lyness, W.I. The effect of methyl-mercapto, methylsulfinyl, and methylsulfonyl groups on the equilibrium in three-carbon prototropic systems. J. Am. Chem. Soc. 1964, 86, 3840–3846.
39. Cilento, G. The expansion of the sulfur outer shell. Chem. Rev. 1960, 60, 147–167.
40. Inomata, K.; Hirata, T.; Suhara, H.; Kinoshita, H.; Kotake, H.; Senda, H. Stereochemistry of the conversion of γ-substituted (E)-vinyl sulfones to the corresponding allyl sulfones. Determination of the relative drgree of syn-effect. Chem. Lett. 1988, 17, 2009–2012.
41. Snyder, H.R.; Eliel, E.L.; Charnahan, R.E. Studies in the sulfone series. J. Am. Chem. Soc. 1951, 73, 3258.

S/N	Compound	Disease Studied	Model	NRF2 Activating Conc/Activity	Mechanism of Action	Biological Activity	Reference
	(vinylsulfinyl)propan-1-ol						
34	 1-(4-fluorophenyl)-3-(vinylsulfinyl)propan-1-ol	Parkinson's disease	BV-2 Cells	20 µM	electrophilic modification of KEAP1 cysteine residues	NRF2 activation, Antioxidant,	[3]

45. Taber, D.F.; Saleh, S.A. Branching strategy in organic synthesis 2-Reveral of olefin polarization with concomitant carbon-carbon bond formation. J. Org. Chem. 1981, 46, 4817–4819.
46. Smith, M.B.; March, J. Advanced Organic Chemistry: Ractions, Mechanism and Structure, 6th ed.; Wiley-Interscience: New York, NY, USA, 2007.
47. Rodrigues, T.; Recker, D.; Schneider, P.; Schneider, G. Counting on natural products for drug design. Nat. Chem. 2016, 8, 531–541.
48. Arshad, L.; Jantan, T.; Bukhari, S.N.A.; Haque, A. Immunosuppressive effects of natural α,β-unsaturated carbonyl-based compounds, and their avalogs and derivatives, on immune cells: A review. Front. Pharmacol. 2017, 8, 22.
49. Snyder, N.W.; Singh, B.; Buchan, G.; O'Brien, J.; Arroyo, A.D.; Liu, X.; Sobol, R.W.; Blair, I.A.; Mesaros, C.A.; Wendell, S.G. Primary saturation of α,β-unsaturated carbonyl containing fatty acid does not abolish electrophilicity. Chem.-Biol. Interact. 2021, 350, 109689.
50. Thapa, P.; Upadhyay, S.P.; Suo, W.Z.; Singh, V.; Gurung, P.; Lee, E.S.; Sharma, R.; Sharm, M. Chalcone and its analogs:therapeutic and diagnostic applications in Alzheimer's disease. Bioorganic Chem. 2021, 108, 104681.
51. Naidu, S.D.; Dinkova-Kostova, A.T. KEAP1, a cysteine-based sensor and a drug target for the prevention and treatment of chronic disease. Open Biol. 2020, 10, 200105.
52. Shin, J.W.; Chun, K.-S.; Kim, D.-H.; Kim, S.-J.; Kim, S.H.; Cho, N.-C.; Na, H.-K.; Surh, Y.-J. Curcumin induces stabilization of Nrf2 protein through Keap1 cysteine modification. Biochem. Pharmacol. 2020, 173, 113820.
53. Grimsrud, P.A.; Xie, H.; Griffin, T.J.; Bernlohr, D.A. Oxidative stress and covalent modification of protein withbioactive aldehydes. J. Biol. Chem. 2008, 283, 21837–21841.
54. Ahn, Y.-H.; Hwang, Y.; Liu, H.; Wang, X.J.; Zhang, Y.; Stephenson, K.K.; Boronina, T.N.; Cole, R.N.; Dinkova-Kostova, A.T.; Talalay, P.; et al. Electrophilic tuning of the chemoprotective natural product sulforaphane. Proc. Natl. Acad. Sci. USA 2010, 107, 9590–9595.
55. Tirumalai, R.; Rajesh, K.T.; Mai, K.H.; Biswal, S. Acrolein causes transcriptional induction of phase II genes by activation of Nrf2 in human lung type II epithelial (A549) cells. Toxicol. Lett. 2002, 132, 27–36.

56. Randall, M.J.; Spiess, P.C.; Hristova, M.; Hondal, R.J.; Vander, A. Acrolein-induced activation of mitogen-activated protein kinase signalling is mediated by alkylation of thioredoxin reductase and thioredoxin1. Redox Biol. 2013, 1, 265–275.

57. Poganik, J.R.; Aye, Y. Electrophilic signaling and emerging immune and neuromodulatory electrophilic pharmaceuticals. Front. Aging Neurosci. 2020, 12, 1.

58. Ploger, M.; Sendker, J.; Langer, K.; Schmidt, T.J. Covalent modification of human serum albumin by the natural sesquiterpene lactone partheolide. Molecules 2015, 20, 6211–6223.

59. Wu, C.C.N.; Rosenbach, M.D.; Corr, M.; Schwab, R.B. Selectivity of electrophilic compounds in chronic lymphocytic leukemia. Proc. Natl. Acad. Sci. USA 2010, 107, 7479–7484.

60. Ghantous, A.; Gali-Muhtasib, H.; Vuorela, H.; Salibba, N.A.; Darwiche, N. What made sequiterpene lactones reach cancer clinical trials? Drug Discov. Today 2010, 15, 668–678.

61. Moujir, L.; Callies, O.; Sousa, P.M.C.; Sharopov, F.; Seca, A.M.L. Applications of sequiterpene lactones: A review of sow potential success cases. Appl. Sci. 2020, 10, 3001.

62. Gach, K.; Dlugosz, A.; Janecka, A. The role of oxidative stress in anticancer activity of sesquiterpene lactones. Naunyn-Schmiedeberg's Arch. Pharmacol. 2015, 388, 477–486.

63. Esatbeyoglu, T.; Obermair, B.; Dorn, T.; Sims, K.; Rimbach, G.; Birringer, M. Sesquiterpene lactone composition and cellular Nrf2 induction of Taraxacum officinale leaves and roots and taraxinic acid β-d-glucopyranosyl ester. J. Med. Food 2017, 20, 71–78.

64. Umemura, K.; Itoh, T.; Hamada, N.; Fujita, Y.; Ako, Y.; Nozawa, Y.; Matsuura, N.; Linuma, M.; Ito, M. Preconditioning by sesquiterpene lactone enhances H2O2-induced NRF2/ARE activation. Biochem. Biophys. Res. Commun. 2008, 368, 948–954.

65. Fischedick, J.T.; Standford, M.; Johoson, D.A.; De Vos, R.C.H.; Todorovic, S.; Banjanac, T.; Verpoorte, R.; Johnson, J.A. Activation of antioxidant response element in mouse primary cortical cultures with sesquiterpene lactose isolated from Tanaetum parthenium. Planta Med. 2012, 78, 1725–1730.

66. Formisano, C.; Rigano, D.; Millan, E.; Munoz, E.; Taglialatela-Scatati, O. Anti-inflammatory sesquiterpene lactones from Onopordum illyricum L. (Asteraceae) an Italian medicinal plant. Fitoterapia 2017, 116, 61–65.

67. Nodwell, M.B.; Menz, H.; Kirsch, S.F.; Sieber, S.A. Rugulactone and its analogue exert antibacterial effects through multiple mechanisms including inhibition of thiamine biosynthesis. ChemBioChem 2012, 13, 1439–1446.

68. Pareek, A.; Suthur, M.; Rathore, G.S.; Bansal, V. Feverfe (Tanacetum parthenium L): A systematic review. Pharmacogn. Rev. 2011, 5, 103–110.

69. Shin, M.; McGonnor, A.; DiNatale, G.J.; Chiramaneqong, T.; Cai, T.; Connor, R.E. Hsp72 is an intracellular target of the α,β-unsaturated sesquiterpene lactone, parthenolide. ACS Omega 2017, 2, 7267–7274.
70. Kupchan, S.M.; Fessler, D.C.; Eakin, M.A.; Giacobbe, T.J. Reactions of alpha methylene lactone tumor inhibitors with model biological neucleophiles. Science 1970, 168, 376–378.
71. Kim, C.Y.; Kang, B.; Hong, J.; Choi, H.-S. Parthenolide inhibits lipid accumulation via activation of NRF2/KEAP1 signaling during adipocyte differentiation. Food Sci. Biotechnol. 2019, 29, 431–440.
72. Kim, C.Y.; Kang, B.; Suh, H.J.; Choi, H.-S. Parthenolide, a fever few-derived phytochemical, ameliorates obesity and obesity-indvied infleammatory responses via the NRF2/Keap pathway. Pharmacol. Res. 2019, 145, 104259.
73. Mao, W.; Zhu, Z. Parthenolide inhibirs hydrogen peroxide-induced osteoblast apoptosis. Mol. Med. Rep. 2018, 17, 8369–8376.
74. Uchi, H.; Arrighi, J.F.; Aubry, J.P.; Furue, M.; Hauser, C. The sesquiterpene lactone parthenolide inhibits LSP- but not TNF-alpha induced maturation of human monocyte-derived dendritic cells by inhibition of the P38 mitogen-activated protein kinase pathway. J. Allergy Clin. Immunol. 2002, 110, 269–276.
75. Hwang, D.; Fischer, N.H.; Jang, B.C.; Tak, H.; Kim, J.K. Inhibition of the expression of inducible cyclooxygenase and proinflammatory cytokines by sesquiterpene lactones in microphags correlates with the inhibition of MAP Kinases. Biochem. Biophys. Res. Commun. 1996, 226, 810–818.
76. Bostwick, D.-G.; Alexander, E.E.; Singj, R.; Shan, A.; Qian, J.; Santella, R.M.; Oberley, L.W.; Yan, T.; Zhong, W.; Jiang, X.; et al. Antioxidant enzyme expression and reactive oxygen species damage in prostatic intraepithelial neoplasia and cancer. Cancer 2000, 89, 123–134.
77. Dey, S.; Sarkar, M.; Giri, B. Anti-inflammatory and anti-tumor activities of parthenolide: An update. J. Chem. Biol. Ther. 2016, 1, 107.
78. Li-Weber, M.; Palfi, K.; Giaisi, M.; Krammer, P.H. Dual role of the anti-inflammatory sesquiterpene lactone: Regulation of life and death by parthenolide. Cell. Death Differ. 2005, 12, 408–409.
79. Carlisi, D.; De Blasio, A.; Drago-Ferrante, R.; Fiore, R.D.; Buttitta, G.; Morreale, M.; Scerri, C.; Vento, R.; Tosoriere, G. Parthenolide Prevents resistance of MDA-MB231 cells to doxorubicin and mitoxantrone: The role of NRF2. Cell. Death Discov. 2017, 3, 17078.
80. Carlisi, D.; Buttitta, R.; Di Fiore, R.; Scerri, C.; Drago-Ferrante, R.; Vento, R.; Tesoriere, G. Parthenolide and DMAPT exert cytotoxic oxidative stress, mitochondrial dysfunction and necrosis. Cell. Death Dis. 2016, 7, e2194.

81. Kriplani, P.; Guarve, K. Recent patents on anti-cancer potential of helenalin. Recent Pat. Anticancer Drug Discov. 2020, 15, 132–142.
82. Shoaib, M.; Shah, I.; Ali, N.; Adhikari, A.; Tahir, M.N.; Shah, S.W.A.; Ishtiag, S.; Khan, J.; Khan, S.; Umer, M.N. Sesquiterpene lactone! A promising antioxidant, anticancer and moderate antinociceptive agent from artemesia macrocephala jacquem. BMC Complement. Altern. Med. 2017, 17, 27.
83. Lyss, G.; Knorre, A.; Schmidt, T.J.; Pahl, H.L.; Merfort, I. The anti-inflammatory sesquiterpene lactone helenaline inhibits the transcription factor NF-kapper B by directly targeting p65. J. Biol. Chem. 1998, 273, 33508–33516.
84. Li, Y.; Zeng, Y.; Huang, Q.; Wen, S.; Wei, Y.; Chen, Y.; Zhang, X.; Bai, F.; Lu, Z.; Wei, J.; et al. Helenalin from centipede minima ameliorates acute hepatic injury by protecting mitochondria function, activating NRF2 pathway and inhibiting NF-kB activation. Biomed. Pharmacother. 2019, 119, 109435.
85. Lin, X.; Zhang, S.; Huang, R.; Wei, L.; Tan, S.; Liang, S.; Tian, Y.; Wu, X.; Lu, Z.; Huang, Q. Helenalin enhancing ethanol metabolism, inhibiting oxidative stress and suppressiong HSC activation. Fitoterapia 2014, 95, 203–213.
86. Chun, J.; Li, R.-J.; Cheng, M.S.; Kim, Y.S. Alantolactone, a sesquiterpene lactone isolated from Inula helenium L. Selectrively suppress STAT3 actyivation and exhibits anticancer activity in MDA-MB-231 cells. Cancer Lett. 2015, 357, 393–403.
87. Kahn, M.; Li, T.; Ahmad, K.M.K.; Rasul, A.; Nawaz, F.; Sun, M.; Zheng, Y.; Ma, T. Alantolactone induces apoptosis in HepG2 cells though GSH depletion, inhibition of STAT3 activation, and mitochondrial dysfunction. Biomed. Res. Int. 2013, 2013, 719858.
88. Huo, J.; Shi, H.M.; Li, W.W.; Wang, M.Y.; Li, X.B. HPLC determination and NMR structural elucidatrion of sesquiterpene lactones in Inula helenuim. J. Pharm. Biomed. Anal. 2010, 51, 942–946.
89. Liu, J.; Liu, M.; Wang, S.; He, Y.; Huo, Y.; Yang, Z.; Cao, X. Alntolactone induces apoptosis and suppresses migration in MCF-7 human breast cancer cells via the p38 MAPK, NF-kB and NRF2 signaling pathways. Int. J. Mol. Med. 2018, 42, 1847–1856.
90. Seo, J.Y.; Lim, S.S.; Kim, J.R.; Lim, J.-S.; Ha, Y.R.; Lee, I.A.; Kim, E.J.; Park, J.H.Y.; Kim, J.-S. NRF2-mediated Induction of detoxifying enxymes by alantolactone present in Invla helenium. Phytother. Res. 2008, 22, 1500–1505.
91. Dang, X.; Holt, B.; Ning, Q.; Liu, Y.; Guo, J.; Niu, G.; Chen, M. Alantolactone suppresses inflammation, apoptosis and oxidative stress in cigarette smoke-induced human bronchial epithelial cells through activation of NRF2/HO-1 and inhibition of the NF-kB pathways. Respirat. Res. 2020, 21, 95.

92. Kim, D.Y.; Choi, B.Y. Costunolide, a bioactive sesquiterpene lactone with diverse therapentic potential. Int. J. Mol. Sci. 2019, 20, 2926.
93. Mao, J.; Yi, M.; Wang, R.; Huang, Y.; Chen, M. Protective effects of costunolide against D-galactos-amine and lipopolysaccharide-induced acute liver injury in mice. Front. Pharmacol. 2018, 9, 1469.
94. Pae, H.O.; Jeong, G.-S.; Kim, H.-S.; Woo, H.Y.; Rhew, H.S.; Kim, D.H.; Sohn, Y.C.; Kim, H.T.; Chung, H.-T. Costunolide inhibits production of tumor necrosis factor- K and interleukin-6 by inducing heme oxygenase-1 in RAW 264-7 Microphages. Inflamm. Res. 2007, 56, 520–526.
95. Eliza, J.; Daisy, P.; Ignacimuthu, S. Antioxidant activity of costunolide and eremanthin isolated from costus speciosus (Ken ex. Retz) sm. Chem. Biol. Interact. 2010, 188, 467–472.
96. Zheng, H.; Chen, Y.; Zhang, J.; Wang, L.; Jin, Z.; Huang, H.; Man, S.; Gao, W. Evaluation of costunolide and dehydrocostulactone on ethano-induced gastric ulcer in mice based on multi-pathway regulation. Chem. Biol. Interact. 2016, 250, 68–77.
97. Peng, S.; Hou, Y.; Yao, J.; Fang, J. Activation of NRF2 by costunolide provides neuroprotective effect in PC12 Cells. Food Funct. 2019, 10, 4143.
98. Mythri, R.B.; Bharath, M.M. Curcumin: A potential neuroprotective agent in Parkinson's disease. Curr. Pharm. Des. 2012, 18, 91–99.
99. Kunnumakkara, A.B.; Bordoloi, D.; Padmavathi, G.; Monisha, J.; Roy, N.K.; Prasad, S.; Aggarwal, B.B. Curcumin, the golden neutraceutical: Multitargeting for multiple chronic disease. Br. J. Pharmacol. 2017, 174, 1325–1348.
100. Rahban, M.; Habibi-Rezaei, M.; Mazaheri, M.; Saso, L.; Moosavi-Movahedi, A.A. Anti-viral potential and modulation of NRF2 by curcumin: Pharmacological implications. Antioxidants 2020, 9, 1228.
101. Madden, S.K.; Itzhaki, L.S. Structural and mechanistic insights into the KEAP1-NRF2 system as a route to drug discovery. Biochim. Et. Biophys. Acta (BBA)-Proteins Proteom. 2020, 1868, 140405.
102. Park, J.-Y.; Sohn, H.-Y.; Koh, Y.H.; Jo, C. Curcumin activates NRF2 through PKCδ-mediated p62 phosphorylation at Ser351. Sci. Rep. 2021, 11, 8430.
103. Ashrafizadeh, M.; Ahmadi, Z.; Mohammadinejad, R.; Farkhondeh, T.; Samarghandian, S. Curcumin activates the NRF2 pathway and induces cellular protection against oxidative injury. Curr. Mol. Med. 2020, 20, 116–133.
104. Gonzalez-Reyes, S.; Guzman-Beltran, S.; Medina-Campos, O.N.; Pedraza-Chaverri, J. Curcumin Pretreatment induces NRF2 and an antioxidant response and prevents Hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats. Oxid. Med. Cell. Longev. 2013, 2013, 801418.

105. Ren, L.; Zhan, P.; Wang, Q.; Wang, C.; Liu, Y.; Yu, Z.; Zhang, S. Curcumin unregulates the NRF2 system by repressing inflammatory signalling-mediated KEAP1 expression in insulin-resistant conditions. Biochem Biophys Res. Commun. 2019, 514, 691–698.

106. Kim, J.S.; Oh, J.-M.; Choi, H.; Kim, S.W.; Kim, B.G.; Cho, J.H.; Lee, J.; Lee, D.C. Activation of the NRF2/HO-1 pathway by curcumin inhibits oxidative stress in human nasal fibroblasts exposed to urban particulate matter. BMC Compl. Med. Ther. 2020, 20, 101.

107. Mishra, P.; Paital, B.; Jena, S.; Swain, S.S.; Kumar, S.; Yadav, M.K.; Chainy, G.B.N.; Samanta, L. Possible activation of NRF2 by vitamin E/curcumin against altered thyroid hormone induced oxidative stress via NFkB/AKT/Mtor/kap1 signaling in rat heart. Sci. Rep. 2019, 9, 7408.

108. Straus, D.S.; Glass, C.K. Cyclopentenone prostaglandins: New insights on biological activities and cellular targets. Med. Res. Rev. 2001, 21, 185–210.

109. Kim, E.H.; Surh, Y.J. 15deoxy-D12,14-prostaglandin J2 as a potential endogeneous regulator of redox-sensitive transcription factors. Biochem. Pharmacol. 2006, 72, 1516–1528.

110. Song, N.-Y.; Kim, E.-H.; Na, H.-K.; Surh, Y.-J. 15-Deoxy-delta 12, 14-prostaglandin J2 induces upregulation of multidrug resistance-associated protein 1 via NRF2 activation in human breast cancer cells. Natural compounds and their role in apoptotic cell signaling pathways. Am. N. Y. Acad. Sci. 2009, 1171, 210–216.

111. Yu, X.; Egner, P.A.; Wakabayashi, J.; Wakabayashi, N.; Yamamoto, M.; Kensler, T.W. NRF2-mediated induction of cytoprotective enzymes by 15-deoxyD1214 –prostaglandin J2 is attenuated by alkenal/one oxidoreductase. J. Biol. Chem. 2006, 281, 26245–26252.

112. Kansanen, E.; Kuosmanen, S.M.; Leinonen, H.; Levonen, A.-L. The KEAP1-NRF2 pathway: Mechanisms of activation and dysregulation in cancer. Redox Biol. 2013, 1, 45–49.

113. Ugwu, D.I.; Ezema, B.E.; Okoro, U.C.; Eze, F.U.; Ekoh, O.C.; Egbujor, M.C.; Ugwuja, D. 1. ChemInform Abstract: Synthesis and pharmacological applications of chalcones: A review. ChemInform 2015, 13, 459–500.

114. Constantinescu, T.; Lungu, C.N. Anticancer activity of natural and synthetic chalcones. Int. J. Mol. Sci. 2021, 22, 11306.

115. Tang, Y.-L.; Zheng, X.; Qi, Y.; Pu, X.-J.; Liu, B.; Zhang, X.; Li, X.-S.; Xiao, W.-L.; Wan, C.-P.; Mao, Z.-W. Synthesis and anti-inflammatory evaluation of new chalcone derivatives bearing bispiperazine linker as IL-1β inhibitors. Bioorganic Chem. 2020, 98, 103748.

116. Ngameni, B.; Cedric, K.; Mbaveng, A.T.; Erdogan, M.; Simo, I.; Kuete, V.; Dastan, A. Design, synthesis, characterization, and anticancer activity of a novel series of O-Substituted chalcone derivatives. Bioorganic Med. Chem. Lett. 2021, 35, 127827.

117. Miranda-sapla, M.M.; Tomiotto-Pellissier, F.; Assolini, J.P.; Carloto, A.C.M.; Bortoleti, B.T.D.S.; Goncalves, M.D.; Tavares, E.R.; Rodrigues, J.H.D.S.; Simao, A.N.C.; Yamauchi, L.M.; et al. Trans-chalcone modulates Leishmania amazonensis infection in vitro by NRF2 over expression affecting iron availability. Eur. J. Pharmacol. 2019, 853, 275–288.

118. Kuhnl, J.; Roggenkamp, D.; Gehrke, S.A.; Stab, F.; Wenck, H.; Kolbe, L.; Neufang, G. Lichochalcone A activates NRF2 in vitro and contributes to licorice extract-induced lowered cutaneous oxidative stress. Exp. Damatol. 2015, 24, 42–47.

119. Zhang, M.; Wu, Y.-Q.; Xie, L.; Wu, J.; Xu, K.; Xiao, J.; Chen, D.Q. Isoliquiritigenin protects against pancreatic injury and intestinal dysfunction after severe acute pancreatitis via NRF2 signaling. Front. Pharmacol. 2018, 9, 936.

120. Yang, H.-L.; Yang, T.-Y.; Gowrisankar, Y.V.; Liao, C.-H.; Liao, J.-W.; Huang, P.-J.; Hseu, Y.-C. Suppression of LPS-induced inflammation by chalcone flavokawain A through activation of NRF2/ARE-mediated antioxidant genes and inhibition of ROS/NFkB signaling pathways in primary splenocytes. Oxid. Med. Cell. Longev. 2020, 2020, 3476212.

121. Fox, R.J.; Miller, D.H.; Phillips, J.T.; Hutchinson, M.; Havrdova, E.; Kita, M.; Yang, M.; Raghupathi, K.; Novas, M.; Sweetser, M.T.; et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N. Engl.J. Med. 2012, 367, 1087–1097.

122. Bomprezzi, R. Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: An overview. Ther. Adv. Neurol. Disord. 2015, 8, 20–30.

123. Bista, P.; Zeng, W.; Ryan, S.; Lukashev, M.; Yamamoto, M. Dimethyl fumarate suppresses inflammation in vitro via both NRF2-dependent and NRF2-independent pathways. Neurology 2012, 78, P02.108.

124. Akino, N.; Wada-Hiraike, O.; Isono, W.; Terao, H.; Honjo, H.; Miyamoto, Y.; Tanikawa, M.; Sone, K.; Hirano, M.; Harada, M.; et al. Activation of NRF2/KEAP1 pathway by oral dimethylfumarate administration alleviates oxidative stress and age-associated infertility might be delayed in the mouse ovary. Reprod. Biol. Endocrinol. 2019, 17, 23.

125. Gopal, S.; Mikulskis, A.; Gold, R.; Fox, R.J.; Dawson, K.T.; Amaravadi, L. Evidance of activation of the NRF2 pathway in multiple sclerosis patients treated with delayed –release dimethyl fumarate in the phase 3 define and confirm studies. Mult. Scler. J. 2017, 2017, 1875–1883.

126. Ahuja, M.; Kaidery, N.A.; Yang, L.; Calingasan, N.; Smirnova, N.; Gaisin, A.; Gaisina, I.N.; Gazaryan, I.; Hushpulian, D.M.; Kaddour-Djebbar, I.; et al. Distinct NRF2 signaling mechanisms of fumaric acid esters and their role in neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced experimental Parkinson's like disease. J. Neurosci. 2016, 36, 6332–6351.

127. Rosto, M.; Testi, C.; Parisi, G.; Cortese, B.; Baiocco, P.; Di Angelantonio, S. Exploring the use of dimethyl fumarate as microglia modulator for neurodegenerative diseases treatment. Antioxidants 2020, 9, 700.

128. Egbujor, M.C.; Okoro, U.C.; Egu, A.S.; Okonkwo, V.I.; Okafor, S.N.; Emeruwa, C.N.; Egwuatu, P.I.; Umeh, O.R.; Eziafakaego, M.I.; Amasiatu, I.S.; et al. Synthesis and biological evaluation of sulfamoyl carboxamide derivatives from sulfur-containing α-amino acids. Chiang Mai J. Sci. 2022, 49, 1100–1115.

129. Strating, J. Organic Sulfur Compounds, 1st ed.; Pergamon Press: Oxford, UK, 1961.

130. Egbujor, M.C.; Okoro, U.C.; Okafor, S. Design, synthesis, molecular docking, antimicrobial and antioxidant activities of new phenylsulfamoyl carboxylic acids of pharmacological interest. Med. Chem. Res. 2019, 28, 2118–2127.

131. Egbujor, M.C.; Okoro, U.C. New methionine-based p-toluenesulphonamoyl carboxamide derivatives as antimicrobial and antioxidant agents: Design, synthesis. J. Pharm. Res. Int. 2019, 28, 1–12.

132. Egbujor, M.C.; Okoro, U.C.; Okafor, S.; Nwankwo, N.E. Design, synthesis and molecular docking of novel serine-based sulphonamide bioactive compounds as potential antioxidant and antimicrobial agents. Attach. Am. J. Pharm. Sci. 2019, 6, 12232–12240.

133. Abdel-Aziz, A.A.; Angeli, A.; El-Azab, A.S.; Hammouda, M.E.A.; El-Sherbeny, M.A.; Supuran, C.T. Synthesis and anti-inflammatory activity of sulphonamides and carboxylates incorporating trimellitimides: Dual cyclooxygenase/carbonic anhydrase inhibitory actions. Bioorganic Chem. 2019, 84, 260–268.

134. Simpkins, N.S. Sulfone in Organic Synthesis, 1st ed.; Pergamon Press: Oxford, UK, 1993.

135. Forristal, I. The chemistry of α,β-unsaturated sulfoxides and sulfones: An update. J. Sulfur Chem. 2005, 26, 163–195.

136. Palmer, J.T.; Rasnick, D.; Klaus, J.L.; Bromme, D. Vinyl sulfones as mechanism-based cysteine protease inhibitor. J. Med. Chem. 1995, 38, 3193–3196.

137. Liu, S.; Hanzlik, R.P. Structure-activity relationship for inhibition of papain by peptide Michael acceptors. J. Med. Chem. 1992, 35, 1067–1075.

138. Engel, J.C.; Doyle, P.S.; Hsieh, I.; Mckerrow, J.H. Cysteine protease inhibitors cure an exprermental trypanosome cruzi infection. J. Exp. Med. 1998, 188, 725–734.

139. Frankel, B.A.; Bentley, M.; Kruger, R.G.; McCatterty, D.G. Vinyl sulfones: Inhibitors of SrtA, a transpeptidase required for cell wall protein anchoring and virvlence in staphylococcus aureus. J. Am. Chem. Soc. 2004, 126, 3404–3405.

140. Roush, W.R.; Gwaltney, S.L.; Cheng, J.; Scheidt, K.A.; Mckerrow, J.H.; Hansell, E. Vinyl sulfonates esters and vinyl sulphonamides: Potent, irreversible inhibitors of cystein proteases. J. Am. Chem. Soc. 1998, 120, 10994–10995.

141. Kover, G.E.; Kam, C.M.; Powers, J.C.; Hudig, D. Dipeptide vinyl sulfones suitable for intracellular inhibition of dipeptidyl peptidase I. Int. J. Immunopharmacol. 2001, 1, 21–32.

142. Kam, C.M.; Gotz, M.G.; Koot, G.; McGuire, M.; Thiele, D.; Hudig, D.; Powers, J.C. Design and evaluation of inhibitors for dipeptidyl peptidase I (Cathepsin C). Arch. Biochem. Biophys. 2004, 427, 123–134.

143. Woo, S.Y.; Kim, J.H.; Moon, M.K.; Han, S.-H.; Yeon, S.K.; Choi, J.W.; Jang, B.K.; Song, H.J.; Kang, Y.G.; Kim, J.W.; et al. Discovery of vinyl sulfones as novel class of neuroprotective agents towards Parkinson’s disease therapy. J. Med. Chem. 2014, 57, 1473–1487.

144. Smith, D.A.; Cucurull-Sanchez, L. The adaptive in combo strategy. In Comprehensive Medicinal Chemistry II; Pfizer Global Research and Developmental: Sandwich, UK, 2007; Volume 5, pp. 957–969.

145. Song, Z.-L.; Hou, Y.; Bai, F.; Fang, J. Generation of potent NRF2 activators via tuning the electrophilicity and steric hinderance of vinyl sulfones for neuroprotection. Bioorganic Chem. 2020, 107, 104520.

146. Egbujor, M.C.; Okoro, U.C.; Okafor, S. Novel alanine-based antimicrobial and antioxidant agents: Synthesis and molecular docking. Indian J. Sci. Technol. 2020, 13, 1003–1014.

147. Egbujor, M.C.; Okoro, U.C.; Nwobodo, D.C.; Ezeagu, C.U.; Amadi, U.B.; Okenwa-Ani, C.G.; Ugwu, J.I.; Okoye, I.G.; Abu, I.P.; Egwuatu, P.I. Design, synthesis, antimicrobial and antioxidant activities of novel threonine-based sulfonamide derivatives. J. Pharm. Res. Int. 2020, 32, 51–61.

148. Onoabedje, E.A.; Ibezim, A.; Okoro, U.C.; Batra, S. Synthesis, molecular docking, antiplasmodial and antioxidant activities of new sulfonamido-peptode derivatives. Heliyon 2020, 6, e04958.

149. Egbujor, M.C.; Okoro, U.C.; Egu, S.A.; Egwuatu, P.I.; Eze, F.U.; Amasiatu, I.S. Design, synthesis and biological evaluation of alanine-based sulphonamide derivatives. Int. J. Res. Pharm. Sci. 2020, 11, 6449–6458.

150. Egbujor, M.C.; Okoro, U.C.; Okafor, S.; Nwankwo, N.E. Synthesis, characterization and in silico studies of novel alkanoylated 4-methylphenyl sulphonamoyl carboxylic acids as potential antimicrobial and antioxidant agents. Int. J. Pharm. Phytopharm. Res. 2019, 9, 89–97.

151. Egbujor, M.C.; Egu, S.A.; Okonkwo, V.I.; Jacob, A.D.; Egwuatu, P.I.; Amasiatu, I.S. Antioxidant drug design:historical and recent developments. J. Pharm. Res. Int. 2021, 32, 36–56.

152. Egbujor, M.C.; Okoro, U.C.; Okafor, S.N.; Amasiatu, I.S.; Amadi, U.B.; Egwuatu, P.I. Synthesis, molecular docking and pharmacological evaluation of new 4-methylphenylsulphamoyl carboxylic

acids analogs. Int. J. Res. Pharm. Sci. 2020, 11, 5357–5366.

153. Luan, F.; Wei, L.; Zhang, J.; MI, Y.; Dong, F.; Li, Q.; Guo, Z. Autioxidant activity of chitosan derivatives with propane sulfonate groups. Polymer 2018, 10, 395.
154. Arshia, A.J.; Faheem, A.; Khan, K.M.; Shah, S.; Perveen, S. Benzophenone esters and sulfonates synthesis and their potential as anti-inflammatory agents. Med. Chem. 2019, 15, 162–174.
155. Gilchrist, T.L. Synthesis: Carbon with three or four attached heteroatoms. In Comprehensive Organic Functional Group Transformations; Elsevier Science: Oxford, UK, 2017; Volume 6.
156. Otacka, S.; Kwiatknowska, M.; Madalinska, L.; Kielbasinski, P. Chiral organosulfur ligands/catalysts with a stereogenic sulfur atom: Applications in asymmetric synthesis. Chem. Rev. 2017, 117, 414–4181.
157. Elisia, I.; Nakamura, H.; Lam, V.; Hofs, E.; Cederberg, R.; Cait, J.; Hughes, M.R.; Lee, L.; Jia, W.; Adomat, H.H.; et al. DMSO represses inflammatory cytokine production from human blood cells and reduces autoimmune arthritis. PLoS ONE 2016, 11, e0152538.
158. Sanmartin-Suarez, C.; Soto-Otero, R.; Sanchez-Sellero, I.; Mendez-Alvarez, E. Antioxidant properties of dimethyl sulfoxide and its viability as a solvent in the evaluation of neuroprotective antioxidants. J. Pharmacol. Toxicol. Methods 2011, 63, 209–215.
159. Forristal, I.; Rayner, C.M. Advances in Sulfur Chemistry. In Recent Advances in the Chemistry of α,β-Unsaturated Sulfoxides and Sulfones; Rayner, C.M., Ed.; JAI Press: Greenwich, CT, USA, 2000; Volume 2, pp. 155–213.
160. Posner, G.H. Asymmetric Synthesis; Morrison, J., Ed.; Academic Press: New York, NY, USA, 1983; Volume 2, p. 225.
161. Lyzwa, P.; Jankowiak, A.; Kwiatowska, M.; Mikolajczyk, M.; Kielbasinski, P.; Betz, A.; Jaffres, P.-A.; Gavmont, A.-C.; Gulea, M. Diastereoselective Michael additions to α,β-unsaturated sulfinyl phosphonates in the thiolane series. Tetrahedron Lett. 2007, 48, 351–355.
162. Unnikrishria, M.K.; Rao, M.N.A. Anti-inflammatory activity of methionine, methionine sulfoxide and methionone sulfone. Agents Actions 1990, 31, 110–112.