

# Sulforaphane and Isothiocyanate Analogues in Cisplatin-Induced Kidney Injury: A Review.

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## Abstract

Cisplatin remains an important antineoplastic agent, but its clinical utility is constrained by dose-limiting nephrotoxicity. The supplied study by Kim et al. reported the synthesis of 16 sulforaphane analogues and their evaluation in cisplatin-treated LLC-PK1 renal epithelial cells. The compounds were prepared from primary amines through dithiocarbamate formation followed by Boc2O/DMAP-mediated conversion to the corresponding isothiocyanates. The analogue series was designed to explore the influence of side-chain lipophilicity, chain length and steric features on cytoprotective activity. Several analogues performed comparably to or better than sulforaphane in the cell-survival assay; notably, SF5 produced approximately 93% cell survival at 2.5  $\mu$ M, while SF6, SF8 and SF13 exceeded 80% survival at 2.5  $\mu$ M. Mechanistic experiments with SF5 associated protection with suppression of the JNK–p53–caspase-3 apoptotic cascade. This focused review reorganizes those findings into a broader medicinal-chemistry and renal-protection framework and incorporates subsequent literature showing that sulforaphane activity is also closely linked to NRF2-dependent antioxidant and cytoprotective signaling. Current evidence therefore supports a multidimensional model in which isothiocyanate structure, electrophilic reactivity, oxidative-stress control and apoptotic signaling collectively determine renoprotective performance. The SF5 series provides a useful starting point for further optimization, but translation requires confirmation in human proximal-tubule models, appropriate animal studies, pharmacokinetic evaluation, and careful assessment of whether renal protection compromises the antitumor activity of cisplatin.

**Keywords:** sulforaphane; isothiocyanates; cisplatin; nephrotoxicity; acute kidney injury; LLC-PK1; JNK; p53; caspase-3; NRF2; structure–activity relationship

## 1. Introduction

Cisplatin-induced renal injury is a major limitation of an otherwise highly effective anticancer drug. The supplied article emphasizes that cisplatin nephrotoxicity involves multiple interacting processes, including reactive oxygen species (ROS), mitogen-activated protein kinase signaling, p53 activation, apoptosis and inflammatory responses. These pathways are not independent: oxidative stress can amplify stress-kinase signaling, mitochondrial dysfunction can promote apoptotic execution, and inflammatory mediators can intensify tubular injury. Contemporary reviews continue to describe cisplatin-associated acute kidney injury as a multifactorial process involving tubular accumulation, DNA damage, oxidative stress, inflammation and apoptosis. [1–4]

The original study was motivated by the observation that sulforaphane, a naturally occurring isothiocyanate derived from cruciferous vegetables, can induce cellular defense systems and protect renal epithelial cells from cisplatin-associated oxidative injury. The investigators therefore used sulforaphane as a chemical template and introduced side-chain variation to search for analogues with improved cytoprotective potency. [1]

Rather than presenting the work as a short communication centered on a single lead compound, the present manuscript places the synthesis, structure–activity relationships (SAR), cellular data and signaling observations within a review framework. The focus is deliberately narrow: synthetic sulforaphane/isothiocyanate analogues and their potential role in mitigating cisplatin-associated renal epithelial injury.

## 2. Sulforaphane as a Chemoprotective Isothiocyanate Scaffold

Sulforaphane is an electrophilic isothiocyanate generated from the glucosinolate glucoraphanin. Its biological effects have been extensively associated with activation of endogenous cytoprotective programs, particularly the KEAP1–NRF2–antioxidant response element axis. NRF2 regulates genes involved in glutathione synthesis, redox homeostasis,

xenobiotic metabolism and cellular stress adaptation, including NQO1, HO-1, glutamate-cysteine ligase and glutathione S-transferases. [5–7]

Importantly, sulforaphane should not be regarded simply as a conventional radical-scavenging antioxidant. Its electrophilic character enables modification of redox-sensitive protein targets and subsequent transcriptional adaptation. This distinction is important when interpreting cisplatin models: protection can reflect reprogramming of cellular defense and stress signaling rather than direct neutralization of every ROS species.

Early experimental work demonstrated that sulforaphane can protect LLC-PK1 cells from cisplatin-induced cytotoxicity and can attenuate renal dysfunction and oxidative/nitrosative stress in animal models. Later studies in human kidney cell systems further supported the protective potential of NRF2 activators, including sulforaphane, and demonstrated increased expression of cytoprotective genes such as GCLC and NQO1. [5,8]

### 3. Pathobiology of Cisplatin-Induced Kidney Injury

Cisplatin-associated kidney injury is centered on the renal tubule, where the drug and its reactive metabolites can accumulate and trigger a network of intracellular stress responses. Current literature describes several overlapping mechanistic components: (i) cellular uptake and transport, (ii) DNA and protein injury, (iii) ROS generation and antioxidant depletion, (iv) mitochondrial dysfunction, (v) inflammatory signaling, and (vi) regulated cell-death pathways including apoptosis. [2–4]

The JNK pathway is particularly relevant to the supplied study. Cisplatin-induced stress was associated with increased JNK phosphorylation, elevated p53 and increased cleavage of caspase-3. In the original experiments, treatment with SF5 reduced these markers in a concentration-dependent pattern, supporting a functional association between the analogue and attenuation of stress-induced apoptosis. [1]

At the same time, a broader interpretation is warranted. Subsequent work has established NRF2 as a major regulator of the renal antioxidant response and has emphasized the interaction of NRF2 with oxidative stress, inflammation, mitochondrial function and cell survival. Thus, the JNK–p53–caspase-3 observations should be viewed as one component of a larger stress-response network rather than as proof that SF5 acts exclusively through this cascade. [6,7]



General two-stage conversion used for the sulforaphane analogue library

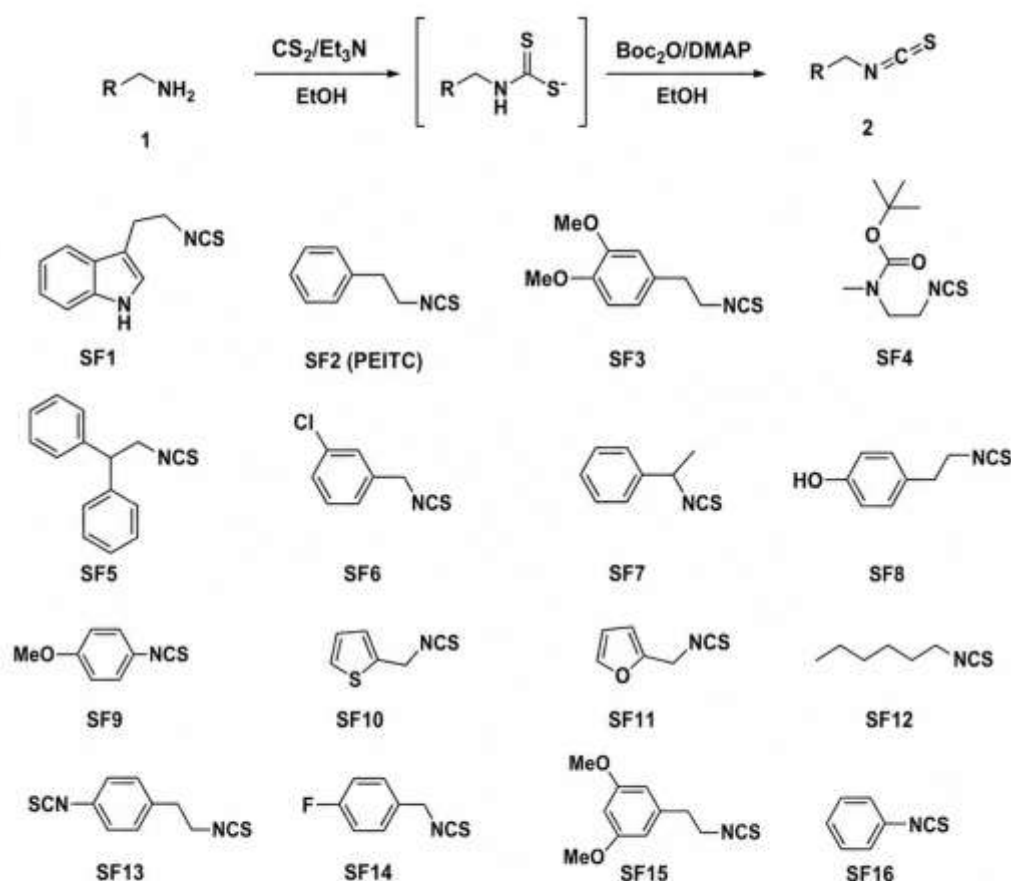


Figure 1. The synthetic scheme of sulforaphane and chemical structure of sulforaphane analogues.

Figure 1. General synthetic strategy used to convert primary amines into the corresponding sulforaphane-type isothiocyanates. The supplied study employed CS<sub>2</sub>/Et<sub>3</sub>N in ethanol to form a dithiocarbamate intermediate, followed by Boc<sub>2</sub>O/DMAP-mediated conversion to the isothiocyanate.

#### 4. Synthetic Strategy for the Sulforaphane Analogue Library

The chemical strategy is concise and modular. Primary amines were treated with carbon disulfide under basic conditions to generate dithiocarbamate intermediates. Subsequent treatment with di-tert-butyl dicarbonate (Boc<sub>2</sub>O) and catalytic 4-dimethylaminopyridine (DMAP) afforded the corresponding isothiocyanates. The method was applied to both aliphatic and aromatic amines, enabling systematic variation of the substituent attached to the isothiocyanate group. Products were purified by silica-gel chromatography and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and LC–MS. [1]

The reported preparation of SF5 illustrates the efficiency of the approach. Starting from 2,2-diphenylethylamine, the authors reported isolation of the isothiocyanate in 97% yield. The reported characterization included <sup>1</sup>H NMR, <sup>13</sup>C NMR and ESI-MS data, providing an analytical basis for assignment of the target structure. [1]

From a medicinal-chemistry perspective, the route is attractive because the amine component can be diversified before the final isothiocyanate-forming step. Such a late-stage diversification strategy is well suited to small SAR libraries, although future optimization should also consider regioselectivity, chemical stability, protein reactivity and metabolic liability of the resulting isothiocyanates.

#### 5. Structure–Activity Relationships

Sixteen sulforaphane analogues (SF1–SF16) were evaluated in the original LLC-PK1 protection assay. The design principles explicitly considered side-chain lipophilicity, chain length and steric effects because these parameters can influence both cellular exposure and the intrinsic reactivity of the isothiocyanate group. [1]

The reported SAR is informative even though the original article was not designed as a formal quantitative QSAR study. Bulky 1-phenylethane and methoxyphenyl substitution was associated with reduced activity, suggesting that steric congestion or unfavorable physicochemical properties can diminish protection. In contrast, chlorobenzyl, hydroxyphenethyl and diphenethyl substitution was tolerated and, in the cases highlighted by the authors, associated with enhanced protection. SF5 was selected for mechanistic investigation because of its strong cellular potency. [1]

| Analogue    | Structural class described in source        | Key reported activity                   | SAR interpretation                                                                               |
|-------------|---------------------------------------------|-----------------------------------------|--------------------------------------------------------------------------------------------------|
| SF1         | Indole-containing / aromatic isothiocyanate | No exact value stated in text           | Aromatic heterocycle tolerated; quantitative comparison should use original figure.              |
| SF2 (PEITC) | Phenethyl isothiocyanate                    | Comparable activity in assay            | Benchmark aromatic ITC; useful comparator for side-chain effects.                                |
| SF3         | Dimethoxyphenethyl-type analogue            | No exact value stated in text           | Electron-rich aromatic substitution; activity not highlighted as a lead.                         |
| SF4         | N-substituted / aliphatic ITC               | No exact value stated in text           | Bulky heteroatom-containing side chain; moderate protection in original screening.               |
| SF5         | 2,2-Diphenylethyl isothiocyanate            | 93% survival at 2.5 $\mu$ M             | Strongest highlighted lead; bulky diaryl-containing side chain was tolerated.                    |
| SF6         | Chlorobenzyl isothiocyanate                 | >80% survival at 2.5 $\mu$ M            | Chloro substituent and benzyl spacer were associated with improved activity.                     |
| SF7         | 1-Phenylethyl-type ITC                      | Reduced activity                        | Steric effect of substituted benzylic center was considered unfavorable.                         |
| SF8         | Hydroxyphenethyl ITC                        | >80% survival at 2.5 $\mu$ M            | Hydroxyl-containing side chain was tolerated and enhanced activity.                              |
| SF9         | Methoxyphenyl ITC                           | Reduced activity                        | Methoxyphenyl substitution was associated with decreased activity, attributed to steric effects. |
| SF10        | Heteroaryl-containing ITC                   | No exact value stated in text           | Heteroaromatic side chain tolerated; not selected as lead.                                       |
| SF11        | Heteroaryl/aliphatic ITC                    | Improved survival at higher tested dose | Activity increased with concentration in the source assay.                                       |
| SF12        | Straight-chain aliphatic ITC                | 90% survival at 10 $\mu$ M              | Simple aliphatic chain provided substantial protection at higher concentration.                  |

|      |                                          |                                    |                                                                                                |
|------|------------------------------------------|------------------------------------|------------------------------------------------------------------------------------------------|
| SF13 | Bifunctional/SCN-containing aromatic ITC | >80% survival at 2.5 $\mu$ M       | Additional thiocyanate functionality was compatible with protection.                           |
| SF14 | Fluorinated aromatic ITC                 | No exact value stated in text      | Fluoro substitution did not emerge as a lead under the reported conditions.                    |
| SF15 | Dimethoxybenzyl-type ITC                 | Improved survival at 2.5 $\mu$ M   | Electron-rich aromatic substitution showed measurable protection but was not selected as lead. |
| SF16 | Phenyl isothiocyanate                    | Improved survival in dose response | Simple aromatic ITC provided a useful structural comparator.                                   |

Table 1. Review-oriented summary of the 16 sulforaphane analogues evaluated in the supplied study. Only activity values explicitly stated in the article text are reported numerically; values not stated in the text are intentionally not reconstructed from the figure.

A central lesson from the series is that increasing lipophilicity does not automatically translate into improved cytoprotection. The diphenethyl-derived SF5 performed particularly well, whereas other aromatic substitutions were less effective. This indicates that an optimal balance among hydrophobicity, steric accessibility, conformational flexibility and electrophilic reactivity may be required. Future studies should quantify these relationships using measured physicochemical descriptors and standardized potency endpoints rather than relying only on categorical SAR.

## 6. Cellular Evaluation and Renoprotective Activity

The biological screen used LLC-PK1 porcine proximal-tubule epithelial cells. Cisplatin at 25  $\mu$ M was used to generate a reproducible cytotoxic stress condition, and cell survival was quantified using the WST-1/CKK-8 assay format. The authors reported approximately 60% survival under the cisplatin condition, providing a window in which protective effects could be detected. Sulforaphane at 10  $\mu$ M increased survival to above 77% with minimal toxicity under the reported conditions. [1]

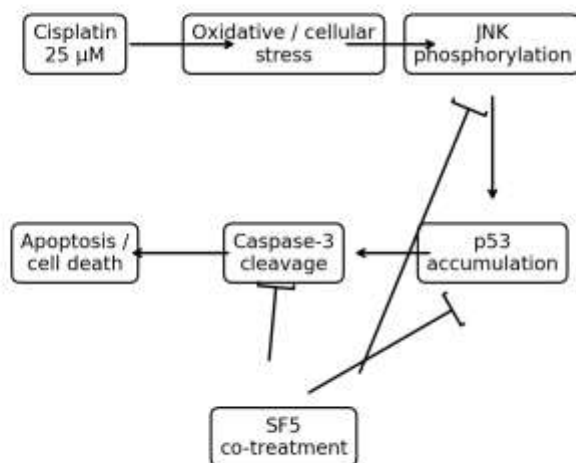
Several analogues showed protection at lower concentrations than sulforaphane. SF6, SF8 and SF13 produced more than 80% survival at 2.5  $\mu$ M, whereas SF5 reached approximately 93% survival at the same concentration. SF12 produced approximately 90% survival at 10  $\mu$ M. These observations support the premise that structural modification of the isothiocyanate side chain can improve apparent cellular potency. [1]

The authors subsequently examined SF5 by microscopy and image-based cytometry. Cisplatin-treated cells displayed growth arrest or cell death, whereas SF5 co-treatment improved apparent cell survival above 1  $\mu$ M. Annexin V/propidium iodide analysis showed that the increased apoptotic population produced by cisplatin was reduced by SF5. The article also states that image-based cytometry results were comparable with independently performed flow-cytometric analysis. [1]

## 7. Mechanistic Basis: JNK–p53–Caspase-3 Signaling

Mechanistic analysis focused on the stress-activated JNK pathway and downstream apoptotic regulators. Western blot analysis showed increased phospho-JNK and cleaved caspase-3 following cisplatin exposure. SF5 reduced phospho-JNK, p53 and cleaved caspase-3 levels in a concentration-dependent pattern, with the most pronounced reduction in p53 reported at 2.5  $\mu$ M SF5. The authors therefore proposed that attenuation of the JNK–p53–caspase-3 cascade contributes to SF5-mediated protection. [1]

### Proposed/observed protective signaling framework



The 2015 study directly linked SF5 protection to reduced phospho-JNK, p53 and cleaved caspase-3. Later work supports a broader antioxidant/NRF2 context.

*Figure 2. Integrated interpretation of the mechanism. The original study directly demonstrated attenuation of phospho-JNK, p53 and cleaved caspase-3 by SF5. The broader oxidative-stress/NRF2 context is supported by subsequent literature and should be considered complementary rather than directly proven for SF5 in the original study.*

The mechanistic evidence should nevertheless be interpreted cautiously. Reduction of pathway markers is consistent with pathway involvement but does not, by itself, establish direct molecular targeting. Stronger causal evidence would require pharmacological inhibition, genetic perturbation or rescue experiments demonstrating that manipulation of JNK or p53 alters SF5 efficacy. The original study therefore provides a plausible signaling mechanism, rather than a complete molecular target identification.

## 8. Integration with Subsequent NRF2 and Renal-Protection Literature

The most important development after the supplied study is the strengthening of evidence for NRF2 as a central regulator of renal antioxidant defense. NRF2 controls a broad cytoprotective transcriptional program, and its loss or inhibition can exacerbate cisplatin-associated renal injury. Reviews published in 2023 emphasize redox regulation of NRF2, its interactions with inflammatory and stress pathways, and the potential and limitations of NRF2-directed interventions. [6,9]

A systematic review and meta-analysis published in 2023 analyzed 25 preclinical studies of sulforaphane in kidney disease models and reported improvements in creatinine clearance, plasma creatinine, urea, proteinuria and several histological or molecular injury measures. These findings support a broad preclinical renoprotective profile for sulforaphane, although they do not establish the clinical efficacy of the SF5 analogue. [10]

Most importantly for the present review, a 2026 study reported that sulforaphane attenuated cisplatin-induced acute kidney injury through effects on oxidative stress, inflammation and apoptosis, with increased NRF2 signaling. In a human HK-2 cell model, inhibition of NRF2 partially reduced the protective effects of sulforaphane, strengthening the case for NRF2-dependent cytoprotection. This newer evidence makes it reasonable to frame the SF5 findings within a broader network linking electrophilic isothiocyanate signaling, NRF2 activation, oxidative-stress control and anti-apoptotic responses. [11]

| Evidence level                       | Model / focus                 | Main finding                                                                                                      | Implication for analogue development                                         |
|--------------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Original analogue study              | LLC-PK1 + cisplatin           | SF5, SF6, SF8 and SF13 showed strong protection; SF5 linked to JNK-p53-caspase-3 attenuation.                     | Supports side-chain optimization and apoptosis-focused screening.            |
| Early sulforaphane studies           | LLC-PK1 and rodent models     | Sulforaphane reduced cisplatin-associated oxidative/nitrosative stress and renal dysfunction.                     | Provides biological rationale for the scaffold.                              |
| Human kidney-cell NRF2 study         | hPTC and HEK293               | Sulforaphane increased cytoprotective genes such as GCLC and NQO1.                                                | Supports translation beyond a single porcine cell line.                      |
| 2023 systematic review/meta-analysis | 25 preclinical kidney studies | Sulforaphane improved multiple renal function and injury outcomes.                                                | Strengthens overall preclinical evidence but not analogue-specific efficacy. |
| 2023 NRF2 review                     | Mechanistic synthesis         | NRF2 integrates redox, inflammatory and cytoprotective signaling in cisplatin injury.                             | Suggests multi-pathway profiling for future analogues.                       |
| 2026 cisplatin-AKI study             | Mouse model + HK-2 cells      | Sulforaphane reduced oxidative stress, inflammation and apoptosis; NRF2 inhibition partially weakened protection. | Supports testing NRF2 dependence of optimized analogues.                     |

Table 2. Evidence hierarchy supporting sulforaphane-based renoprotection and its relevance to the analogue series.

## 9. Limitations of the Current Evidence

Although the original findings are promising, several limitations should be addressed before the compounds can be considered translational candidates. First, the primary screening model was a single immortalized renal epithelial cell line. Species differences and cell-line-specific responses can limit extrapolation to human proximal tubules. Second, the cisplatin concentration of 25  $\mu$ M is a controlled experimental stressor and should not be interpreted as a direct surrogate for human renal exposure.

Third, the study emphasizes cell survival and selected apoptosis markers, but does not provide a complete assessment of renal function, tubular injury biomarkers, mitochondrial function, inflammatory cytokines, oxidative damage, or long-term recovery. Fourth, the original study did not establish the pharmacokinetic properties, metabolic stability, protein reactivity, or in vivo exposure of SF5. Fifth, the possibility that a cytoprotective isothiocyanate could also protect tumor cells from cisplatin requires explicit evaluation. This issue is particularly important because pathways such as ROS, p53 and apoptosis are also central to the antitumor action of cisplatin. [3,4]

Finally, the original mechanistic data demonstrate pathway-associated changes rather than a definitive direct target. For publication in a medicinal-chemistry or pharmacology journal, a stronger evidence chain would connect analogue structure to cellular exposure, molecular target engagement, pathway modulation and a reproducible pharmacodynamic endpoint.

## 10. Future Perspectives and Research Directions

- Expand the SAR library around SF5 by independently varying aryl substitution, spacer length, conformational rigidity, polarity and electron-withdrawing/electron-donating character.
- Determine quantitative potency parameters such as EC50/IC50, maximum protective effect, therapeutic index and a renal-cell selectivity index rather than relying primarily on single concentrations.
- Compare SF5 and optimized analogues in human proximal-tubule models, including HK-2 cells and, where feasible, primary human renal epithelial cells or organoid systems.
- Directly test NRF2 dependence using genetic knockdown/knockout or validated NRF2 inhibitors, while simultaneously measuring NQO1, HO-1, GCLC/GCLM and glutathione status.
- Map the relationship among NRF2, JNK, p53 and caspase-3 to determine whether SF5 acts upstream of JNK, in parallel with NRF2 activation, or through multiple convergent stress pathways.
- Evaluate mitochondrial membrane potential, ATP status, ROS generation, lipid peroxidation, DNA damage and inflammatory mediators to obtain a systems-level profile of renoprotection.
- Establish pharmacokinetic and metabolic profiles, including plasma stability, microsomal stability, glutathione reactivity and tissue distribution.
- Test the most promising analogue in validated cisplatin-AKI animal models with renal function biomarkers, histopathology and dose-response relationships.
- Critically determine whether the analogue preserves cisplatin antitumor efficacy in tumor-bearing models; renoprotection should not be pursued at the expense of chemotherapy effectiveness.
- Explore formulation and delivery approaches that could improve renal exposure while minimizing systemic off-target reactivity.

## 11. Conclusion

The supplied study provides a compact but useful example of how a natural isothiocyanate scaffold can be transformed into a small analogue library to address cisplatin-associated renal cytotoxicity. The modular CS2/Boc2O/DMAP synthetic sequence enabled preparation of 16 sulforaphane-type isothiocyanates, and the resulting SAR demonstrated that side-chain architecture strongly influences cytoprotective activity. SF5 emerged as the most compelling analogue in the reported screen, producing approximately 93% cell survival at 2.5  $\mu$ M and reducing apoptosis-associated signaling in cisplatin-treated LLC-PK1 cells. [1]

From a current perspective, the significance of the work extends beyond the original JNK–p53–caspase-3 observation. Subsequent research has reinforced the importance of NRF2-mediated antioxidant and cytoprotective signaling in cisplatin kidney injury and has continued to support sulforaphane as a promising preclinical renoprotective agent. Accordingly, future sulforaphane analogue development should integrate medicinal chemistry, quantitative SAR, NRF2 pharmacology, stress-kinase biology, pharmacokinetics and tumor-sparing efficacy. SF5 should therefore be regarded as a valuable lead structure for further investigation rather than as a clinically validated nephroprotective drug.

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