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# Identification of a novel orally bioavailable NLRP3 inflammasome inhibitor

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ABSTRACT

NLRP3 inflammasome mediated release of interleukin-1β (IL-1β) has been implicated in various diseases, including COVID-19. In this study, rationally designed alkenyl sulfonylurea derivatives were identified as novel, potent and orally bioavailable NLRP3 inhibitors. Compound **7** was found to be potent (IL-1β $IC_{50}$ = 35 nM; IL-18 $IC_{50}$ = 33 nM) and selective NLRP3 inflammasome inhibitor with excellent pharmacokinetic profile having oral bioavailability of 99% in mice.

Coronavirus disease 2019 (COVID-19), a pandemic caused by SARS-CoV2 virus has gripped > 200 countries of the world infecting > 20 million people and causing death of over 900,000 worldwide.[1] While most of the infected people regain immune function from initial insult by the virus with mild symptoms, patients with comorbid complications have developed severe clinical conditions with sustained levels of viral load. Severe COVID-19 is characterized by acute respiratory distress syndrome (ARDS) and multiple organ failure possibly caused by uncontrolled immune response in the host. Innate immune response is the first line of defense, warding off the invading pathogens with the help of pattern recognition receptors and the adaptive immune responses through generation of specific antibodies against the pathogens. The major cellular component of adaptive response, namely the lymphocytes are suppressed by SARS-CoV2 leading to lymphocytopenia.[2] This suggests that the uncontrolled immune response observed in severe COVID-19 patients might be resulting mainly from innate immune cells, monocytes, macrophages and neutrophils. The increased levels of inflammatory cytokines released by these cells are the key players in triggering the cytokine storm and ARDS.

Existing evidence shows that severe COVID-19 patients had increased IL-1β and other cytokines in their serum.[3] In light of this observation, therapies targeting neutralization of individual cytokines responsible for cytokine storm are being explored.[4,5] Among others, Anakinra, a recombinant human IL-1 receptor antagonist, in a retrospective cohort study of patients with COVID-19 and ARDS, managed with non-invasive ventilation outside of the ICU with clinical improvement in 72% of the patients.[6] The key pro-inflammatory cytokine, IL-1β is processed and released from neutrophils and monocytes following the formation of an intracellular immune complex called NLRP3 inflammasome. NLRP3 is activated by PAMPS (pathogen associated molecular patterns) and ionic flux in the cells where it oligomerizes, associates with ASC and activates the caspase-1 leading to the release of active pro-inflammatory cytokines, IL-1β and IL-18.[7] Active caspase-1 can also trigger pyroptosis, a highly inflammatory driven cell death triggered by infection through orchestration with caspase-11 to protect the cells from pathogens.[8] However, increased expression of caspase-1 could cause uncontrolled cell death, one of the features observed with ARDS. NLRP3 plays a dual role in activating the cytokines as well as inducing apoptosis in pathological conditions.

Thus, targeting NLRP3 could provide a beneficial strategy in anti-immune therapy regimen over individual cytokines as it can also suppress the ARDS associated apoptosis. Further, a small molecule NLRP3 inhibitor could demonstrate a superior effect compared to IL-1β antibodies. An accelerated exploration of this in clinical studies might provide the much needed plausible treatment option for patients affected by COVID-19 infection worldwide.

*Abbreviations:* NLRP3, NOD-like receptor family, pyrin domain-containing protein 3; AIM2, absent in melanoma 2; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; LPS, Lipopolysaccharide; ATP, adenosinetriphosphate; NCE, new chemical entity; LDA, lithium diisopropylamide; TFA, trifluoroacetic acid; tPSA, total polar surface area; PK, pharmacokinetic

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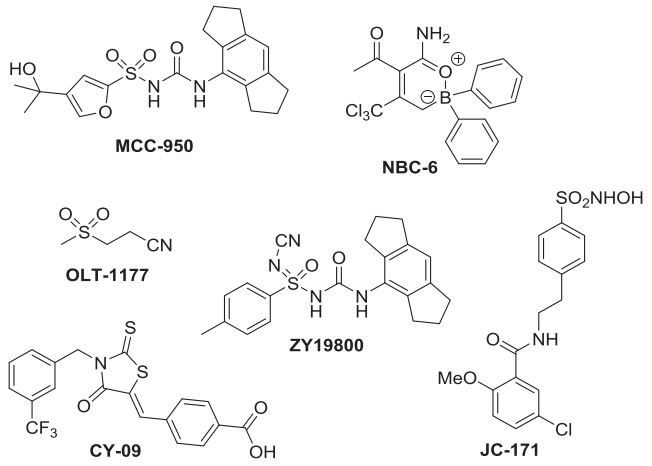



**Fig. 1.** Selected known NLRP3 Inflammasome Inhibitors.

Additionally, NLRP3 inflammasome is evolving as a promising target for treatment of various complex inflammatory and autoimmune diseases.[9] Several structurally diverse small molecule modulators of NLRP3 have been described (Fig. 1).[10] MCC950[11] (also known as CRID3 and CP-456773) a small molecule inhibitor of NLRP3 inflammasome was tested in phase II clinical trials for rheumatoid arthritis but was not developed further as it was found to elevate serum liver enzyme levels in the clinic.[12] In addition, novel boron compound (NBC-6),[13] sulfonamide (JC-171)[14] and compounds like CY09[15], OLT1177[16], Oridonin[17] and Tranilast[18] have also been reported as NLRP3 inflammasome inhibitors. Recently we have reported the discovery of a novel *N*-cyano-sulfoximineurea derivative ZY19800 as potent and orally bioavailable NLRP3 inflammasome inhibitor.[19]

Expansion of the chemical pool with novel compounds for NLRP3 inflammasome inhibitors could increase the possibility for finding potential drug candidates. We present herein, the identification and pharmacokinetic evaluation of novel thiazolo-alkenyl sulfonylurea derivative **7** as potent, selective and orally bioavailable NLRP3 inflammasome inhibitor. High oral bioavailability is an important consideration for the development of bioactive molecules as therapeutic agents. We introduced an alkenyl group which resulted in structurally novel NLRP3 inflammasome inhibitors with improved properties (Fig. 2).[20]

Accordingly, a series of novel alkenyl sulfonylurea derivatives have been synthesized and ability of these test compounds to inhibit NLRP3 inflammasome was assessed in IL-1β assay using THP-1 cells.[11] The Table 1 describes the structure–activity relationship (SAR) of replacement of left-hand side group. The most studied NLRP3 inhibitor, MCC950 was found to be potent with $IC_{50}$ of 8 nM. As we sought to introduce the alkenyl group, the MCC950 equivalent version, represented as compound **2** was the first one synthesized and evaluated in IL-1β assay. However, **2** was found to exhibit $IC_{50}$ of 208 nM. The metabolically reactive furan moiety is a known cause for drug-induced liver injury. Hence, we replaced the furan moiety of MCC950 with various bioisosteric heterocyclic ring systems. The thiophene analogues **3** and **4** were potent with $IC_{50}$ of 70 nM and 96 nM respectively. The 4-pyridine derivative **5** was 164 nM while 2-pyridine analogue **6** had

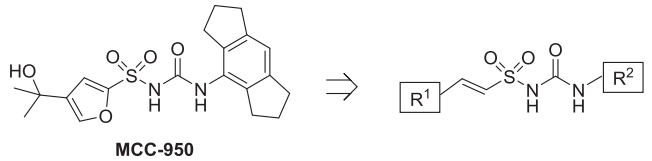
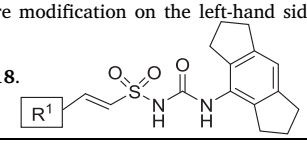
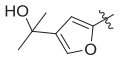
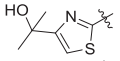
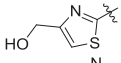
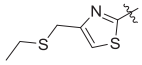
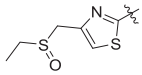
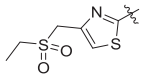
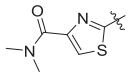
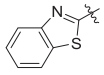



**Fig. 2.** Schematic representation of ligand optimization.

**Table 1**
Core modification on the left-hand side: *In vitro* activity of MCC950 (**1**) and **2–18**.



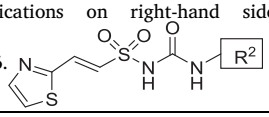
| Compound | $R^1$ | IL-1β $IC_{50}$[a] (nM) | CLogP[b] | tPSA[b] |
|---|---|---|---|---|
| **1 (MCC950)** | | 8 | 3.27 | 104.73 |
| **2** |  | 208 | 3.52 | 104.73 |
| **3** |  | 70 | 3.93 | 75.27 |
| **4** |  | 96 | 3.53 | 75.27 |
| **5** |  | 164 | 5.25 | 87.63 |
| **6** |  | 1000 | 4.39 | 87.63 |
| **7** |  | 35 | 2.31 | 87.63 |
| **8** |  | 76 | 2.94 | 87.63 |
| **9** |  | 1061 | 2.23 | 87.63 |
| **10** |  | 126 | 4.14 | 87.63 |
| **11** |  | 369 | 4.34 | 87.63 |
| **12** |  | 142 | 3.78 | 107.86 |
| **13** |  | 306 | 3.44 | 107.86 |
| **14** |  | 93 | 3.35 | 87.63 |
| **15** |  | 243 | 2.45 | 104.7 |
| **16** |  | 79 | 2.15 | 121.77 |
| **17** |  | 344 | 3.33 | 107.94 |
| **18** |  | > 1000 | 4.52 | 87.63 |

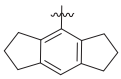
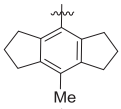
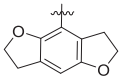
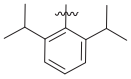
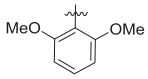
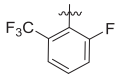
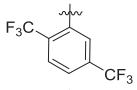
[a] n = 1; [b]Calculated from ChemBioDraw Ultra 16.0.

lower activity. Interestingly, thiazole compound **7** displayed IL-1β inhibition $IC_{50}$ of 35 nM. Having good potency of **7**, further thaizole analogues were evaluated. Introduction of methyl group at 4-position of thiazole (**8**) was tolerated ($IC_{50}$ = 76 nM), however, significant drop in potency was observed for 5-methyl analogue **9** ($IC_{50}$ = 1061 nM). Regioisomers of **7**, compounds **10** and **11** were also relatively less potent. Next, to assess the effect of polarity, carbinol **12** and **13** were synthesized and were found to show $IC_{50}$ of 142 nM and 306 nM respectively. Further, sulfur containing side chain analogue **14** was 93 nM, and its corresponding sulfoxide (**15**) and sulfone (**16**) were found to be 243 nM and 79 nM respectively. Amide substitution of thiazole (**17**) was also tolerated. However, fused heterocyclic system (**18**) resulted in loss of activity with less than 50% inhibition of secreted IL-1β at 1 μM (Table 1).

(E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethene-1-sulfonamide (**7**) was next evaluated for inhibition of IL-1β released with NLRP3 inflammasome activation in THP-1

**Table 2**
Modifications on right-hand side of **7**: *In vitro* activity of **7**, **19–26**.



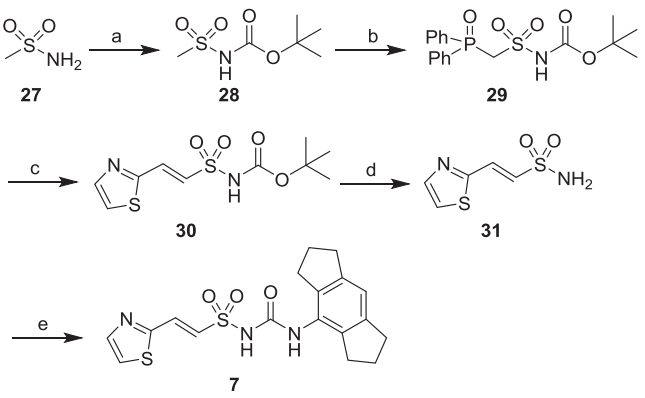
| Compound | $R^2$ | IL-1β $IC_{50}$ (nM)[a] | CLogP[b] | tPSA[b] |
|---|---|---|---|---|
| **7** |  | 35 | 2.31 | 87.63 |
| **19** |  | 294 | 3.86 | 87.63 |
| **20** |  | > 1000 | 1.59 | 106.09 |
| **21** |  | > 1000 | 4.19 | 87.63 |
| **22** |  | > 1000 | 1.47 | 106.09 |
| **23** |  | > 1000 | 2.99 | 87.63 |
| **24** |  | > 1000 | 3.82 | 87.63 |
| **25** |  | > 1000 | 2.75 | 87.63 |
| **26** |  | > 1000 | 3.23 | 87.63 |

[a] n = 1; [b]Calculated from ChemBioDraw Ultra 16.0.

cells using nigericin & MSU and was found to be potent in both the assays with $IC_{50}$ of 26 and 24 nM, respectively (Table S1). Furthermore, **7** was also evaluated in IL-18 assay, which showed dose-dependent IL-18 inhibition with $IC_{50}$ 0f 33 nM. Notably, **7** was highly selective against TNF-α ($IC_{50}$ > 10 μM). The production of TNF-α was not affected by **7** even at high concentration (Figure S5), indicating its selective activity towards NLRP3 inflammasome. Moreover, **7** blocked the oligomerisation of ASC during NLRP3 activation. Furthermore, this compound had no effect on the AIM2 inflammasome, demonstrating specificity among inflammasomes (Figure S6).

Encouraged by the result for **7** we sought to assess the right-hand side tricyclic fragment. Accordingly, we synthesized a small set of compounds that maintained the features of hexahydroindacene ring (Table 2). 4-Methyl tricyclic analogue **19** showed a modest level of inhibition compared with **7**, while conversion to the oxa-ring yielded only inactive compound (**20**). Bis-alkyl and alkoxy substituted phenyls (**21** and **22**), did not give promising results. Further, *ortho*-substituted compounds **23**, **24** and **25** were also resulted in ablation of activity. Finally, tetra-methyl substituted analogue **26** that mimic the hexahydroindacene, resulted in complete loss of potency. Surprisingly, apart from 4-methyl tricyclic analogue **19**, all other right-hand side variations, compounds **20–26**, resulted in loss of activity with less than 50% inhibition of IL-1β release at 1 μM (Table 2). These results indicates the critical importance of the tricyclic ring system topography such that any modification on the right hand side in **7** resulted in loss of NLRP3 inhibition activity.

An efficient synthetic route was developed for **7** as depicted in Scheme 1. The key intermediate **29** was obtained from commercially available methyl sulfonamide (**27**) using known procedure.[21] Horner reaction[22] of **29** with 2-thiazolecarboxaldehyde afforded **30** in good




**Scheme 1.** Synthesis of Compound **7**. *Reagents and conditions*: (a) $(Boc)_2O$, trimethylamine, dichloromethane, 0 °C to r.t., 16 h (100%); (b) LDA, dry THF, −78 °C, $Ph_2POCl$, −78 °C to r.t.,4h (84%); (c) 2-Thiazolecarboxaldehyde, sodium hydride, dry DMF, 0 °C to r.t., 4 h (64%); (d) TFA, dichloromethane, r.t., 4 h (84%); (e) 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (**33**), sodium hydride, dry DMF, 0 °C to r.t., 16 h (32%).

yield. It is noteworthy to mention that, the Boc-sulfonamide **30** had *trans* orientation about the double bond as determined by NMR coupling constants and was isolated essentially as single *E*-isomer; the *cis* isomer was not observed, which is in agreement with literature.[21] This adduct was deprotected using trifluoroacetic acid to provide sulfonamide **31** in 84% yield. Another key intermediate, tricyclic amine (1,2,3,5,6,7-hexahydro-s-indacen-4-amine) (**32**), and its corresponding isocyanate **33**, were synthesized using reported protocol on multi gram scale.[23] The coupling of sulfonamide **31** with 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (**33**) provided sulfonylurea **7**.[24] Following the same reaction sequence with various aldehydes resulted in test compounds **2–18**. While, coupling of sulfonamide **31** with different substituted isocyanates afforded compounds **19–26** in good yield and high chemical purity.

Compound **7** was next evaluated for physiochemical properties and metabolic stability assays in addition to *in vivo* pharmacokinetic profile. Notably, **7** have good aqueous solubility and acceptable lipophilicity with cLogP in the ideal range and low total polar surface area. Furthermore, the compound was found to be metabolically stable in mouse, rat, dog and human liver microsomes and also demonstrated good Caco2 permeability (Table S5). These drug-like properties of compound **7** further enabled its potential for *in vivo* pharmacokinetic profiling.

The *in vivo* pharmacokinetic investigation in C57BL/6 mice revealed that **7** exhibited good oral absorption showing Cmax of 8.49 μg/mL with an AUC of 48.9 μg.h/mL and terminal half-life of 2.86 h, after oral route of administration at 3 mg/kg dose (Table 3). Pharmacokinetic studies in C57BL/6 mice showed a fast oral absorption, higher plasma exposure, and an acceptable half-life and demonstrated an excellent oral bioavailability of 99%.

Evaluation of a drug candidate against the cytochrome P450 (CYP450) enzymes, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 is an important aspect of drug discovery and development.[25] Although **7** has excellent pharmacokinetics profile, it does inhibit both CYP2C8 and CYP2C9, which precludes it from further progression for further *in vivo* efficacy studies. Nonetheless, our chemically driven approach has afforded an orally bioavailable NLRP3 inhibitor. The added *in vitro* characterization of potency, selectivity and the robust evidence in various assay systems, provide a comprehensive data package supporting the use of **7** in future NLRP3 pharmacological investigations. These NLRP3 inflammasome inhibitors with novel chemical structure having high potency and excellent PK profile would be helpful in further investigations as potential clinical candidates.

**Table 3**
Pharmacokinetic[a] profile of MCC950 and **7**.

| Compound | MCC950 | 7 |
|---|---|---|
| Species | Mouse | Mouse |
| PO Dose (mg/kg) | 3 | 3 |
| Tmax (h) | 0.25 | 0.25 |
| Cmax (ng/mL) | 11,731 | 8488 |
| AUC (0-t) (ng.h/mL) | 46,897 | 48,937 |
| T½,po (h) | 1.32 | 2.86 |
| MRT (h) | 3.07 | 4.9 |
| IV Dose (mg/kg) | 1 | 1 |
| $C_0$ (ng/mL) | 22,244 | 6266 |
| AUC (0-t) (ng.h/mL) | 20,667 | 16,452 |
| Vss (L/kg) | 0.15 | 0.2 |
| CL (ml/min/kg) | 0.8 | 1.01 |
| T½, iv (h) | 3.97 | 2.35 |
| MRT (h) | 3.22 | 3.23 |
| %F | 77 | 99 |

[a] Compounds **MCC950** and **7** dosed 1 mg/kg iv and 3 mg/kg po. Mouse PK data is mean data because of composite study design, n = 3/time point. Formulation: PO, 1% Tween 80 + 99% (0.5%) methyl cellulose in water; IV, 5% NMP + 5% solutol + 90% normal saline.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127571.

## References

1. WHO. Coronavirus disease 2019 (COVID-19) situation report – 209. August 16, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200401-sitrep-72-covid-19.pdf?sfvrsn=3dd8971b_2.
2. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID19: Neutrophil extra-cellular traps. *J Exp Med.* 2020;217. https://doi.org/10.1084/jem.20200652.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
4. Michot J-M, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. *Ann Oncol.* 2020;31(7):961–964. https://doi.org/10.1016/j.annonc.2020.03.300.
5. Feldmann M, Maini RN, Woody JN, Holgate ST, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet.* 2020;395(10234):1407–1409. https://doi.org/10.1016/S0140-6736(20)30858-8.
6. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol.* 2020. https://doi.org/10.1016/S2665-9913(20)30129-6.
7. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med.* 2015;21:677–687.
8. He Y, Hara H, Núñez G. Mechanism and Regulation of NLRP3 Inflammasome Activation. *Trends Biochem Sci.* 2016;41(12):1012–1021.
9. Shen H-H, Yang Y-X, Meng X, Luo X-Y, et al. NLRP3: A promising therapeutic target for autoimmune diseases. *Autoimmun Rev.* 2018;17(7):694–702.
10. Shao BZ, Xu ZQ, Han BZ, Su DF, Liu C. Nlrp3 inflammasome and its inhibitors: A review. *Front Pharmacol.* 2015;6:262–271.
11. Coll RC, Robertson AA, Chae JJ, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nat Med.* 2015;21:248–255.
12. Mangan MSJ, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. *Nat Rev Drug Discov.* 2018;17:588–606.
13. Baldwin AG, Rivers-Auty J, Daniels MJD, et al. Boron-Based Inhibitors of the NLRP3 Inflammasome. *Cell Chemical Biology.* 2017;24(11):1321–1335.e5.
14. Guo C, Fulp JW, Jiang Y, et al. Development and characterization of a hydroxyl-sulfonamide analogue, 5-chloro-n-[2-(4-hydroxysulfamoyl-phenyl)-ethyl]-2-methoxy-benzamide, as a novel nlrp3 inflammasome inhibitor for potential treatment of multiple sclerosis. *ACS Chem Neurosci.* 2017;8:2194–2201.
15. Jiang H, He H, Chen Y, et al. Identification of a selective and direct NLRP3 inhibitor to treat inflammatory disorders. *J Exp Med.* 2017;214:3219–3238.
16. Marchetti C, Swartzwelter B, Gamboni F, et al. OLT1177, a beta-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation. *Proc Natl Acad Sci.* 2018;115:E1530–E1539.
17. He H, Jiang H, Chen Y, et al. Oridonin is a covalent nlrp3 inhibitor with strong anti-inflammasome activity. *Nat Commun.* 2018;9:2550.
18. Huang Y, Jiang H, Chen Y, et al. Tranilast directly targets nlrp3 to treat inflammasome-driven diseases. *EMBO Mol Med.* 2018;10:e8689–8704.
19. Agarwal S, Sasane S, Shah HA, et al. Discovery of *N*-Cyano-sulfoximineurea derivatives as potent and orally bioavailable NLRP3 inflammasome inhibitors. *ACS Med Chem Lett.* 2020;11:414–418.
20. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem.* 2002;45:2615–2623.
21. Reuter DC, McIntosh JE, Guinn AC, Madera AM. Synthesis of vinyl sulfonamides using the horner reaction. *Synthesis.* 2003(15):2321–2324. https://doi.org/10.1055/s-2003-41059.
22. Horner L, Hoffmann H, Wippel HG, Klahre G. Phosphororganische verbindungen, XX. Phosphinoxyde als olefinierungsreagenzien. *Chem Ber.* 1959;92:2499–2505.
23. Urban FJ, Jasys VJ, Raggon JW, et al. Novel synthesis of 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[4-(1-hydroxy-1-methyl-ethyl)-furan-2-sulfonyl]-urea, an anti-inflammatory agent. *Synth Commun.* 2003;33:2029–2043.
24. (E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethene-1-sulfonamide (7): White powder; mp: 196 °C; % purity: 96.61% (UPLC); 1H NMR (400 MHz, DMSO-d6): δ = 10.63 (br s, 1H,), 8.22 (s, 1H), 8.05 (d, J = 3.2 Hz, 1H), 8.01 (d, J = 3.2 Hz, 1H), 7.74 (d, J = 15.2 Hz, 1H), 7.60 (d, J = 15.2 Hz, 1H), 6.95 (s, 1H), 2.79 (t, J = 7.2 Hz, 4H), 2.66 (t, J = 7.2 Hz, 4H), 1.94 (quin, J = 7.2 Hz, 4H); 13C NMR and DEPT (100 MHz, DMSO-d6): δ = 160.9 (C), 150.1 (C), 145.3 (C), 143.5 (CH), 137.7 (C), 132.9 (CH), 130.4 (CH), 129.2 (C), 125.1 (CH), 118.4 (CH), 32.9 (CH2), 30.7 (CH2), 25.5 (CH2); ESI-Q-TOF-MS: m/z [M+H]+ calcd for [C18H20N3O3S2]+: 390.0946; found: 390.0937; IR (KBr): ν = 3232 ν(N-H), 2949ν(CH2), 1662 ν(C=O), 1552 ν(N-H), 1463 ν(CH2), 1346 ν(CH3), 1151 ν(S=O) cm-1.
25. Kumar GN, Surapaneni S. Role of drug metabolism in drug discovery and development. *Med Res Rev.* 2001;21(5):397.