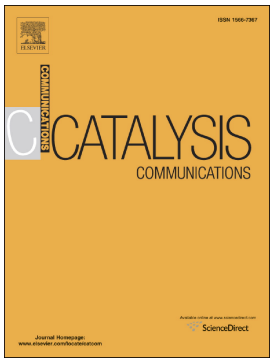

Mo(VI) complex catalysed synthesis of sulfonees and their modification for anti-HIV activities

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Mo(VI) complex catalysed synthesis of sulfones and their modification for anti-HIV activities

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Abstract

An efficient method for the synthesis of sulfones has been developed using sugar derived *cis*-dioxo molybdenum(VI) complex as catalyst and urea hydrogen peroxide as oxygen source. Present method is highly specific for sulfide oxidation irrespective of presence of alkene and aldehyde groups in the same molecule. Synthesis of fifteen sulfones have been reported with 82 – 98 % isolated yields and the catalyst has been reused five times without any loss in its activity. 2-(Phenylsulfonyl)aniline has been condensed with eight different aromatic aldehydes and the products are being explored for HIV-1 reverse transcriptase inhibition activities.

Keywords

Molybdenum; Homogeneous catalysis; Sulfide oxidation; Sulfones; Anti-HIV agent.

1. Introduction

Organic sulfones are one of the important classes of molecules that have been used in various fields like medicine [1], agrochemicals [2], electronics [3], polymers [4], etc. Therapeutic application of sulfones has been started with Promin (sodium glucosulfone) for treating leprosy [5]. Currently, several sulfone containing drugs are available in the market, including Dapsone [6] for leprosy, Casodex [7] for prostate cancer, Relpax [8] for migraine, etc. Diaryl sulfone derivatives like 2-amino-6-arylsulfonylbenzonitrile, pyrrylarylsulfone and indolylaryl sulfones have been reported to inhibit HIV-1 reverse transcriptase (RT) enzyme [9]. Besides biological and pharmaceutical applications, sulfones have also been used in organic synthesis to form heterocycles [10] and stereo selective *C–C* bonds [11]. Owing to their implication in various fields of science, several methodologies have been developed to synthesize the sulfones *via C–S* coupling or oxidation of sulfides [12]. Direct *C–S* coupling approach provides a broad substrate scope; however, its major drawbacks are harsh reaction conditions and low atom economy [13]. An alternate method of sulfone synthesis is oxidation of sulfides using oxidants like potassium permanganate, hydrogen peroxide, oxone and *m*-chloroperoxybenzoic acid in presence/absence of metal catalysts [12]. Recently we have reported *cis*-di-oxo molybdenum(VI) complex catalyzed oxidation of organic sulfides to sulfoxides using one equivalent of urea hydrogen peroxide (UHP) as oxygen source [14] and noticed the formation of sulfone in presence of excess of oxidising agent. Versatile use of sulfones inspired us to develop its synthetic methodology using our catalyst and explore the activity of the resultant molecules. Along this line, we have optimised the conditions for synthesis of sulfone using thioanisole and following the optimum conditions, fifteen molecules have been prepared. One of these sulfones has also been condensed with aromatic aldehydes to form a series of new molecules having imine linkage and evaluation of their anti-HIV abilities are under progress.

Hence, this article presents the optimized conditions for Mo(VI) complex catalyzed synthesis of sulfones along with recyclability of the catalyst, synthesis of imine derivatives of 2-(phenylsulfonyl)aniline and *in silico* evaluation of the resultant molecules as an anti-HIV agent.

2. Experimental

The catalyst (D-glucose derived *cis*-dioxo molybdenum(VI) complex) [15] and selected sulfide derivatives (for entry **O6**-**O9** [16]**, O10** [17]**, O11** [18] and **O12** [19] under Table 2) were prepared following the reported procedure.

2.1 General procedure for catalytic oxidation of organic sulfides to sulfones

Organic sulfide (1.0 mmol), UHP (5.0 mmol) and catalyst (0.05 mmol) were stirred in ethanol (5 mL) at room temperature and the progress of the reaction was monitored using thin layer chromatography (TLC). After completion of the reaction, precipitate formed was filtered off, washed with cold ethanol and dried to obtain the pure organic sulfone. In case of soluble organic sulfones, solvent was evaporated under reduced pressure; residue was triturated with dichloromethane (5 mL) and filtered to remove the insoluble urea and catalyst. The filtrate containing sulfone was dried and recrystallized from dichloromethane/hexane mixture.

*2.2 Synthesis of **N1**-**N8** by condensation of 2-(phenylsulfonyl)aniline (**N0**) with aromatic aldehydes*

2-(Phenylsulfonyl)aniline (1.0 mmol) and aromatic aldehyde (1.02 mmol) were refluxed in ethanol (5 mL) for 8 hours. Solid product formed was filtered and washed with cold ethanol to afford the pure desired compound.

In the case of benzaldehyde, toluene (5 mL) was used instead of ethanol and reaction mixture was refluxed for 24 hours. After cooling the reaction mixture, solvent was evaporated, residue was triturated with hexane and filtered to obtain the pure solid product.

Single crystals suitable for X-ray diffraction studies were generated by layering technique with solvent combinations dichloromethane/hexane for **N3** and **N5**, while dimethyl sulfoxide/methanol for **N8**.

3. Results and discussion

3.1 Oxidation of organic sulfides to sulfones

Catalytic activities of sugar derived molybdenum complexes are limited and we have noticed reports on epoxidation [20, 21], sulfoxidation [14] and bis(indolyl)methanes [22] synthesis. Fridgen et al. [20] and Sui et al. [21] have explored the epoxidation reactions using *tert*-butylhydroperoxide and cumene hydroperoxide respectively as oxidants while Mohammadnezhad et al. used hydrogen peroxide to achieve sulfoxidation. Recently, we have explored Mo(VI) complex catalysed oxidation of organic sulfides to sulfoxides and stability of the catalyst [23]. The robust nature of the catalyst and versatile use of sulfones prompted us to explore the conditions for selective oxidation of sulfides to sulfones and along this line, we performed several control reactions on thioanisole as summarized in Table 1. The progress of the reaction was monitored using TLC and the formation of products was confirmed by HRMS analysis. Catalyst (5 mol%) and five equivalents of UHP with respect to substrate were found to be suitable for sulfone formation under normal conditions and shorter reaction time (15 Min).

Under optimum reaction conditions, fifteen aliphatic and aromatic sulfides, including amino acid (methionine), were oxidized to sulfones in good to excellent isolated yields (82-98%). The details of sulfone formation are summarized in Table 2, which clearly supports the negligible effect of aromatic substituents on reaction time and yield. The reaction proceeds with sulfoxide intermediate and solubility of this intermediate affect the overall reaction time. This fact

was established while monitoring the reactions for the formation of **O4** and **O5** with respect to others. Since excess of UHP was used during the reaction, stability and reusability of catalyst was one of the major concerns and the same was tested on 2-(phenylthio)aniline as substrate. After completion of reaction, solid sulfone was isolated through filtration and the filtrate was charged with fresh substrate and UHP for next cycle. This procedure was repeated for five times and sequential yield was recorded as 92, 98, 97, 97 and 98 % respectively, confirming the stability and reusability of the homogeneous catalyst. A slight increase in the yields of sulfone during the recycling process may be attributed to the saturation of the mother liquor with sulfone after the first cycle. Our protocol is suitable for gram-scale synthesis as we performed the oxidation of 2-(phenylthio)aniline in 3 g scale and isolated corresponding 3.4 g sulfone (**N0**; 98%).

As oxidation of sulfide to sulfones is a well-established reaction, we compared our methodology with the existing reports. A handful of literature reports are available on molybdenum compound catalysed sulfones synthesis using oxidants like hydrogen peroxide [24-27]. The major demerits of these syntheses include complexity in synthesizing the catalysts, elevated temperatures, long reaction time and use of column chromatography for product purification, which restricts gram scale synthesis. Reports are also available on UHP assisted sulfone production in combination with volatile and unstable acid anhydrides [28]. To the best of our knowledge, only one report is available on molybdenum-UHP combination for synthesizing di-*n*-pentyl, methylphenyl and diphenyl sulfones [29]. The major demerit of the procedure mentioned in this paper is the decomposition of catalyst due to the excess oxidant used during the reaction. Hence, our method has several advantages like short reaction time (15 minutes), recyclable catalyst and applicability in large scale synthesis. This method has excellent chemoselectivity towards sulfide group over various other functional groups like alkene, aldehyde, amine, etc. as no side products were formed during oxidation of sulfide substrates containing these functional groups. Oxidation reactions were also set on styrene and 4-chlorobenzaldehyde under optimised reaction condition (using Mo(VI) catalyst and 5 equivalent

UHP) and progress of reaction was monitored. We did not observe any oxidation reaction in either case even after 24 hours, which confirms the chemoselectivity.

*3.2 Synthesis of **N1**-**N8** by condensation of **N0** with aromatic aldehydes*

Compounds **N1**-**N8** were synthesized by condensing **N0** with aromatic aldehydes, as described in section 2.2. FTIR spectral analysis of compounds **N1**–**N7**, revealed strong absorbance in the range of 1600–1625 cm^{-1} and 1145–1155 cm^{-1} corresponding to $\nu_{C=N}$ stretching and $\nu_{S=O}$ symmetric stretching respectively. Proton NMR spectra of these compounds showed singlet peaks corresponding to imine C**H** around δ 8-9 ppm and phenolic O**H** above δ 12 ppm. All these results supported the formation of anticipated products and further confirmation was accomplished by HRMS data along with single-crystal X-ray diffraction studies of **N3** and **N5** (Fig. 1(a) and 1(b)). Analogous reaction with 2-carboxybenzaldehyde afforded cyclized product (**N8**) instead of expected Schiff base and similar report is also available in literature [30]. Racine reported the structure of condensed product to be open-chain Schiff base [31], which was challenged by Kubota et al. [32]. Our finding aligns with the result reported by Kubota et al. and we succeeded in establishing the structure of this molecule using single-crystal X-ray diffraction studies. The crystallographic data confirms the lactam structure (Fig. 1(c)) with C(Ar)–N and C(Lactam)–N bond distances 1.383(2) and 1.417(2) Å respectively. The ∠C(1)N(1)C(9) is found to be 122.26(13)°, which may be attributed to the planar geometry about nitrogen due to the involvement of lone pair electrons in resonance with the aromatic ring. This resonance is further supported by the shorter bond distance between C(Ar)–N, which was noticed by Odabasoglu et al. [33], while solving the structure of 3-anilinoisobenzofuran-1(3H)-one.

3.3 In silico HIV-1 RT inhibition study

McMahon et al. in 1993 illustrated the *in vitro* HIV-1 RT inhibition potential of several diphenyl sulfones wherein nitro derivatives were more active than amine derivatives [34]. Recently GlaxoSmithKline group patented the amide derivative of 2-(phenylsulfonyl)aniline consisting of tetrazole moiety for treating HIV [35]. Since our compounds (**N0**-**N8)** have similarity in structure with above mentioned active compounds, out of curiosity, we are exploring the HIV-1 RT inhibition capability of these molecules. In this direction, we started with *in silico* docking study using Schrödinger software (details provided in supplementary information section 3.1). Docking results (Fig. 2) of synthesised compounds are comparable with that of the commercially marketed drug Rilpivirine. Notably, binding energies (-10.07 to -12.16 kcal/mol) for modified compounds (**N1**-**N8**) are more than that of starting sulfone (**N0**, -8.39 kcal/mol). The highest binding energy (-12.16 kcal/mole) was obtained for methoxy derivative (**N3**), while it is –14.26 kcal/mole for Rilpivirine under identical conditions.

4. Conclusion

This is the first report, where sugar derived molybdenum(VI) complex has been used as a catalyst for selective synthesis of sulfones. The catalyst is stable and reusable in presence of excess (5 equivalents) of urea hydrogen peroxide and the method of transformation is mild. The reactions have been carried out at room temperature in ethanol, and 82–98 % isolated yield of sulfones was recorded within 15 minutes. The catalyst combination is highly specific for sulfide oxidation irrespective of presence of alkene and aldehyde groups; however, hydrolysis of imine bond has been noticed for sulfides having this functionality. One of the catalysed products containing amine group has also been condensed with aromatic aldehydes to generate a series of new molecules and currently we are exploring their anti-HIV activities. Here we are also reporting brief outcome of our *in silico* result in this direction along with crystal structures of three synthesised compounds.

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Appendix A. Supplementary material

Supplementary information including details of synthesis, analytical data, details of *in silico* studies, ^{1}H, ^{13}C NMR spectra, crystallographic data and docking poses of N3 and Rilpivirine along their interactions with wild HIV-1 RT enzyme can be found online at xxxxxxxx. Crystallographic data of **N3**, **N5** and **N8** have been deposited to Cambridge Crystallographic Data Centre and their CCDC deposition numbers are 1968356, 1966960 and 1966961 respectively.

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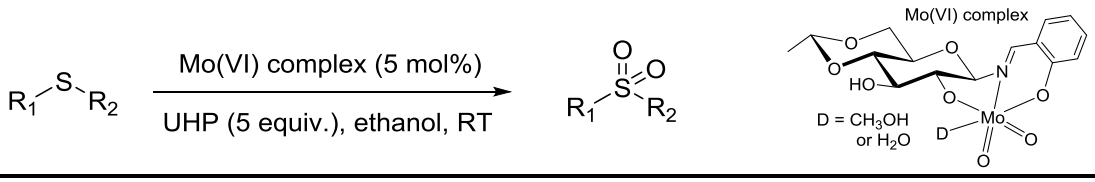
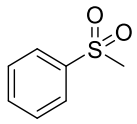
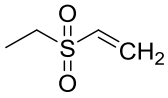
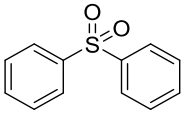
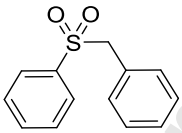
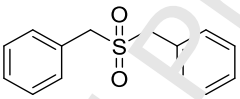
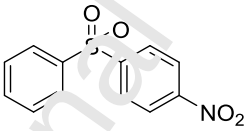
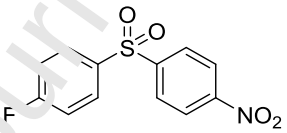
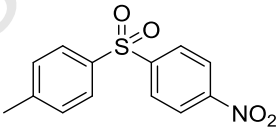
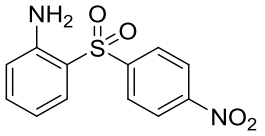
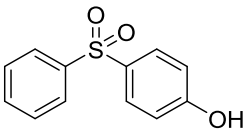
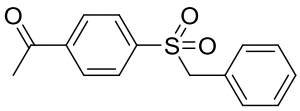
Table 1. Optimization of reaction conditions for selective oxidation of thioanisole to methylphenyl sulfone

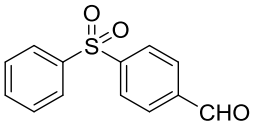
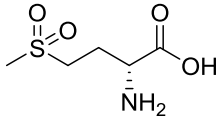
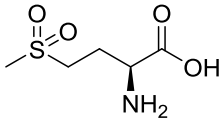
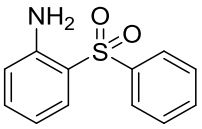
S. No.	Catalyst (% mol)[a]	UHP (equivalents)[a]	Time (Hr)	Sulfone (% yield)[b]	Sulfoxide (% yield)[b]
1	5	1	4	trace	92
2	5	2	4	13	81
3	5	3	4	42	51
4	5	5	0.25	92	trace
5	5	7	0.25	93	trace
6	0	5	24	0	trace
7	1	5	8	88	<5
8	2	5	4	87	<5
9	3	5	1	94	trace
10	10	5	0.25	91	trace

[a] *with respect to sulfide substrate(0.001 mol)* [b] *isolated yields*

Table 2. Sulfone synthesis using Mo(VI) complex–UHP system in ethanol using optimised conditions



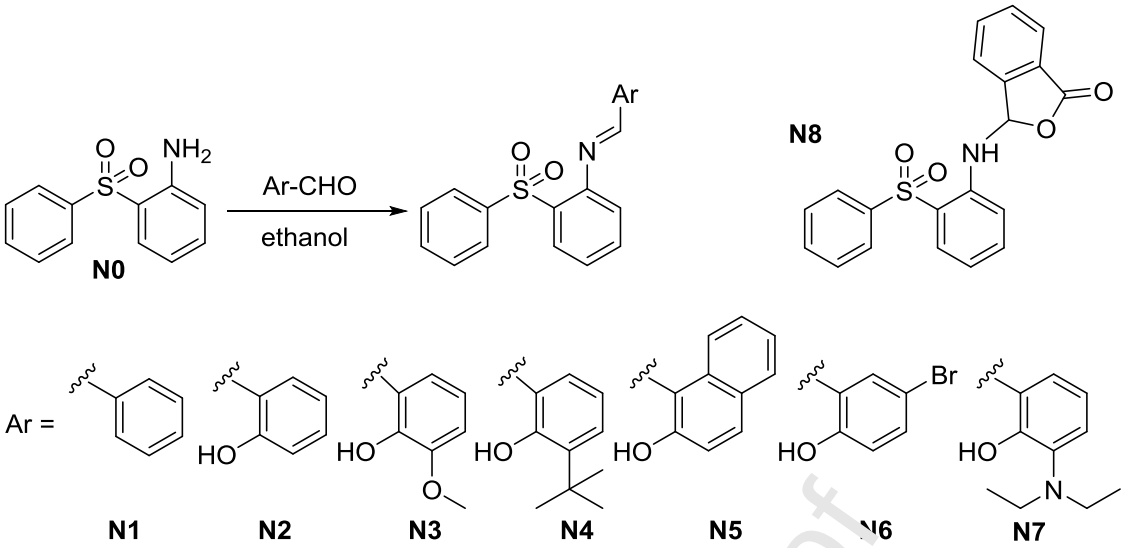
Entry	Sulfone	Yield %[a]
O1		92
O2		95
O3		82
O4		87[b]
O5		86[b]
O6		90
O7		88
O8		93
O9		94
O10		93
O11		97

O12		92
O13		93
O14		91
N0		98[c]

[a] isolated yields after 15 minutes

[b] isolated yields after 30 minutes

[c] 3 g of 2-(phenylthio)aniline was taken



Scheme 1. Synthesis of **N1**-**N8** by condensation of **N0** with aromatic aldehydes.

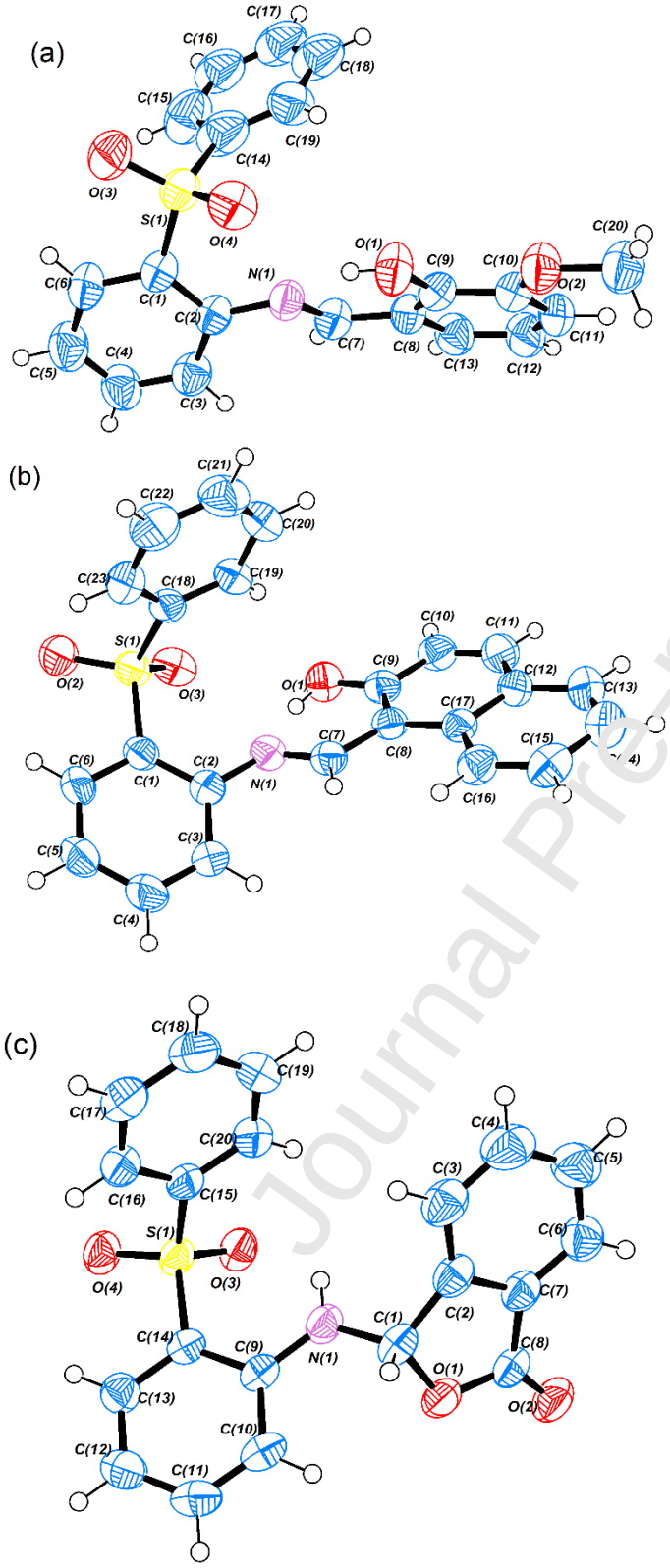


Fig. 1. ORTEP diagrams of (a) **N3**, (b) **N5** and (c) **N8** with 50% thermal ellipsoid probability**.**

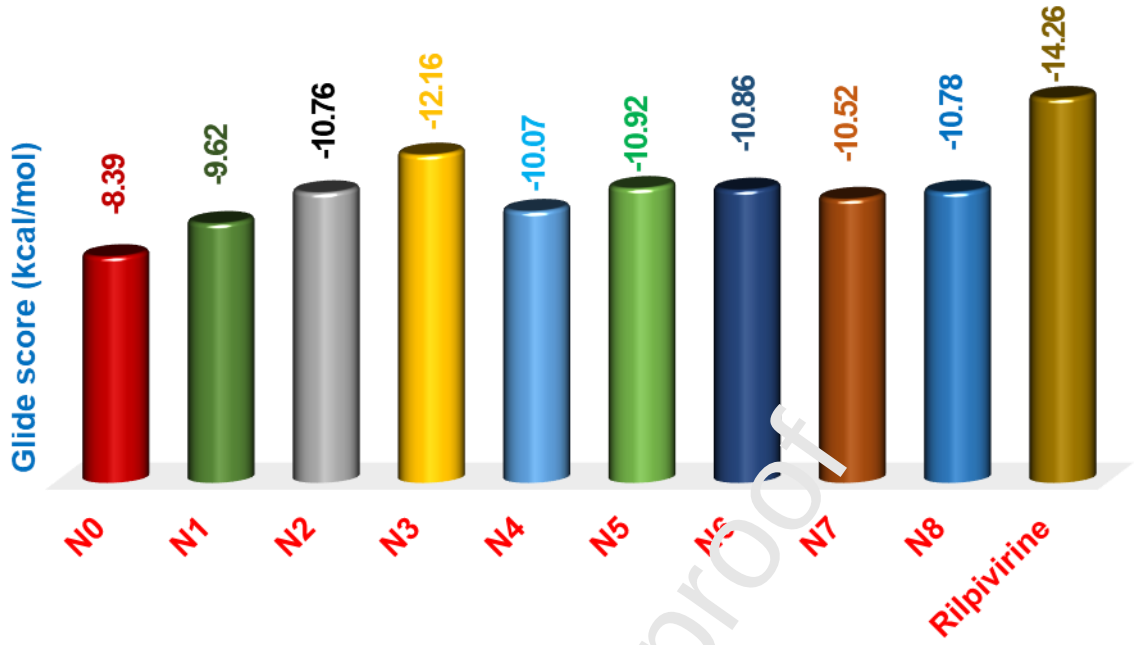


Fig. 2. Glide scores for compounds **N0**-**N8** and co-crystallised ligand (Rilpivirine) when docked in the HIV-1 RT enzyme (PDB ID: 3MEE).

CRediT author statement

Vimal Kumar Madduluri: Conceptualization, Methodology, Investigation, Data curation, Writing- Original draft preparation

Noorullah Baig: Conceptualization, Methodology

Subhash Chander: Software, Investigation

Sankaranarayanan Murugesan: Validation, Writing- Original draft preparation, Supervision

Ajay K. Sah: Validation, Writing- Reviewing and Editing, Supervision, Project administration

Declaration of interests

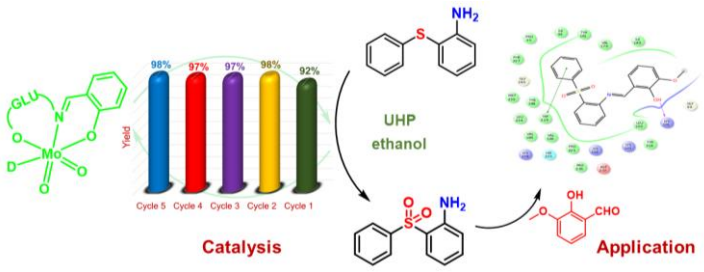
☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Declarations of interest: none

Mo(VI) complex catalysed synthesis of sulfones and their modification for anti-HIV activities

Vimal Kumar Madduluri[a], Noorullah Baig[a], Subhash Chander[b], Sankaranarayanan Murugesan[b] and Ajay K. Sah[a*]



Highlights

- First report on selective sulfone synthesis using D-glucose derived Mo(VI) catalyst
- Gram scale synthesis through homogenous catalysis using UHP as oxygen source
- Catalyst has been recycled for five times without appreciable loss in activity
- Structure of three sulfones has been established using X-ray crystallographic data