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Wang-OSO_3H catalyzed green synthesis of bioactive isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives: An unexpected observation

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ABSTRACT

The sulphonic acid-functionalized Wang resin (Wang-OSO_3H) was explored as a polymeric and recoverable acidic catalyst for the synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives under green conditions. Thus the Wang-OSO_3H catalyzed MCR of isatoic anhydride, 2-formylbenzoic acid and various amines in pure water afforded a range of desired product in good to excellent (86–94%) yield. The methodology can be performed under open air and is amenable for scale-up synthesis. The catalyst can be recovered and recycled for several times without significant loss of its catalytic activity. The unexpected formation of 2-(1–hydroxy-3-oxoisoindolin-2-yl)benzamide derivative as observed in one case may allow the access of this class of heterocycles from the same MCR by using an appropriate amine. *In silico* assessment suggested that the compound **4j**, a known inhibitor of TNF-α could be a potential ligand for SARS-CoV-2 with which it formed H-bonds through its OMe and two C=O groups.

1. Introduction

The 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11–dione framework **A** (Fig 1) has attracted considerable interest due to the interesting pharmacological and other properties shown by compounds containing this scaffold. For example, isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives have been explored as inhibitors of TNF-α (Tumor Necrosis Factor-alpha) [1] in addition to their uses as efficient stabilizers of organic materials against degradation caused by heat, light and/or oxidation [2]. Notably, TNF-α inhibitors are known to be useful for the treatment of several inflammatory disorders such as rheumatoid arthritis, Crohn's disease, and ulcerative colitis [3–6]. Recently, compounds based on **A** have been reported to be inhibitors of PDE 7A (phosphodiesterase 7A), a promising target for the identification of new anti-inflammatory agents with minimal side effects [7]. Nevertheless, very recently the potential of anti-TNF therapy to inhibit the development of a cytokine storm in patients with coronavirus disease 2019 (COVID-19) has been described [8]. While cytokines provide the first line of defense against viruses, the high circulating levels of these cytokines e.g. (IL)−2, IL-6, IL-7, IL-10 etc. including TNF also cause illness as often observed in case of severe form of COVID-19 (that clinically described as the consequence of a cytokine storm frequently). Being the known inhibitors of TNF-α, compounds based on **A** are expected to play a key role in attenuating the cytokine storm in COVID-19. Interestingly, a separate study has suggested that this class of compounds could be potent and selective inhibitors targeting hepatitis B virus [9]. All these reports and observations as well as our interest in developing TNF-α / PDE-4 inhibitors [10,11] or other agents as prospective ligands for SARS-CoV-2 [12,13] we focused on exploring the potential of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives further against COVID-19. We therefore required a convenient access to this class of compounds for conducting related pharmacological studies.

The commonly used routes towards the synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives are summarized in Scheme 1 where 2-formylbenzoic acid (**C**) appeared as a key reactants in most of the cases. Thus the reaction of **C** with 2-aminobenzamides (**B**) or 2-aminobenzohydrazides in different

Abbreviations: MCR, Multi component reaction.

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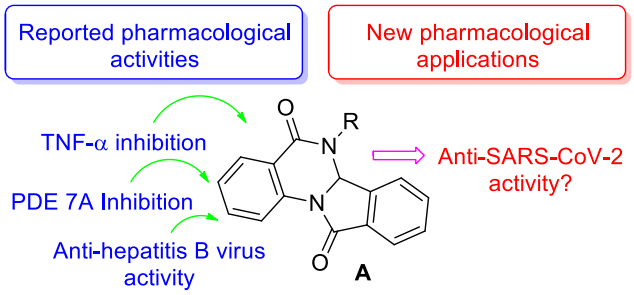
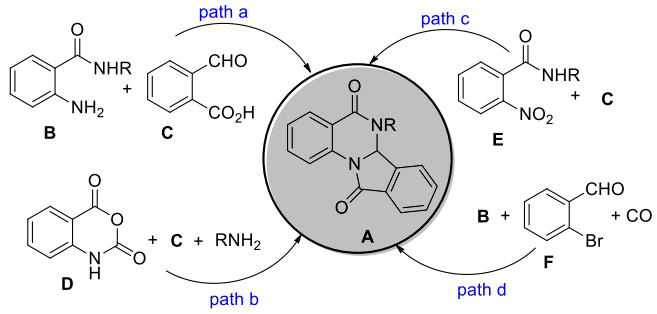
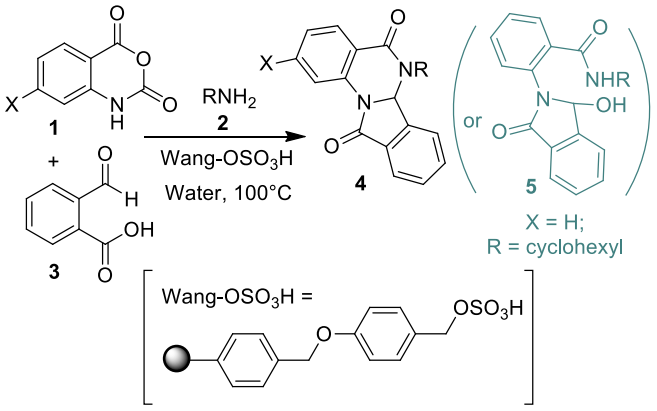


Fig. 1. The proposed and new pharmacological applications of compounds containing 6,6*a*-dihydroisoindolo[2,1-*a*]quinazoline-5,11–dione framework **A** and their known activities.



Scheme 1. Reported methods for the synthesis of compound **A**.

solvents proceeded *via* a cascade pathway to afford **A** (path a, Scheme 1) [14]. The participation of **C** in a 3-component reaction with isatoic anhydride (**D**) and amines afforded **A** separately under various conditions (path b, Scheme 1) [1,9,15]. The MCR (multi component reaction) was also successful when **C** was replaced by 3-bromoisobenzo-furan-1(3*H*)-one without requiring the use of any catalyst or reagent [16]. In another approach **C** along with 2-nitrobenzamides (**E**) participated in a one-pot reduction/cyclization cascade reaction in the presence of a reducing agent e.g. $SnCl_2$ or Fe etc. to give **A** (path c, Scheme 1) [17]. Recently, a Pd-catalyzed one-pot 3-component cascade reaction of **B** with 2-bromobenzaldehydes (**F**) and CO under atmospheric pressure has been developed to afford **A** (path d, Scheme 1) [18]. Several of these methods appeared to be elegant and effective in synthesizing a wide range of desired compounds based on **A**.



Scheme 2. Synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives (**4**) and compound **5** under green reaction conditions.

While some of these reactions can be carried out under environmentally friendly or even catalyst / reagent free conditions the other methods often involve the use of complex or expensive catalysts (that need to be prepared in some cases) or reactants. More importantly, the recovery and recyclability of the catalyst used was either not efficient or remained underexplored in several cases that otherwise is considered as one of the key requirements towards fulfilling the green chemistry conditions. In our effort we have previously reported sulphonic acid-functionalized Wang resin (Wang-OSO_3H) as a polymeric and recoverable acidic catalyst under green conditions [19]. In order to achieve an alternative but green synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives (**4**) *via* the 3-component reaction (path b, Scheme 1) of **1, 2** and **3** we decided to explore the use of same catalyst and water as a solvent (Scheme 2). Herein, we describe not only the details of this study but also formation of an unexpected product i.e. 2-(1–hydroxy-3-oxoisoindolin-2-yl)benzamide derivative (**5**, Scheme 2) in two cases. Additionally, the preliminary *in silico* assessment of the products obtained as potential ligands for SARS-CoV-2 is presented. To our knowledge the use of resin bound Wang-SO_3H as an effective catalyst for the green synthesis of compound **4** or **5** is not common in the literature.

Table 1
Effect of reaction conditions on the MCR of **1a, 2a** and **3**.[a]

Entry	Catalyst (% w/w)	Solvent	T (°C); t (h)	Yield[b] (%)
1.	Amberlite IR120H (10)	H_2O	100; 16	40
2.	$NaHSO_3$–SiO_2 (10)	H_2O	100; 16	35
3.	INDION 225H (10)	H_2O	100; 16	65
4.	PMA-SiO_2 (10)	H_2O	100; 16	50
5.	Wang Resin (10)	H_2O	100; 8	94
6.	Wang Resin (10)	PEG-400	100; 8	86
7.	Wang Resin (10)	PEG-200	100; 8	80
8.	Wang Resin (10)	Ethylene glycol	100; 8	78
9.	Wang Resin (10)	EtOH	90; 8	76
10.	Wang Resin (10)	1,4-Dioxane	100; 8	68
11.	Wang Resin (10)	MeCN	80; 8	65
12.	Wang Resin (5)	H_2O	100; 8	85
13.	No catalyst	H_2O	100; 24	20
14.	Wang Resin (15)	H_2O	100; 8	92
15.	Wang Resin (20)	H_2O	100; 8	92

(Wang Resin = resin bound Wang-OSO_3H).
[a] All the reactions were carried out using isatoic anhydride **1a** (1.0 mmol), 2-methoxyaniline **2a** (1.0 mmol), 2-formylbenzoic acid **3** (1.1 mmol), and catalyst in a solvent (4 mL) under open air.
[b] Isolated yield.

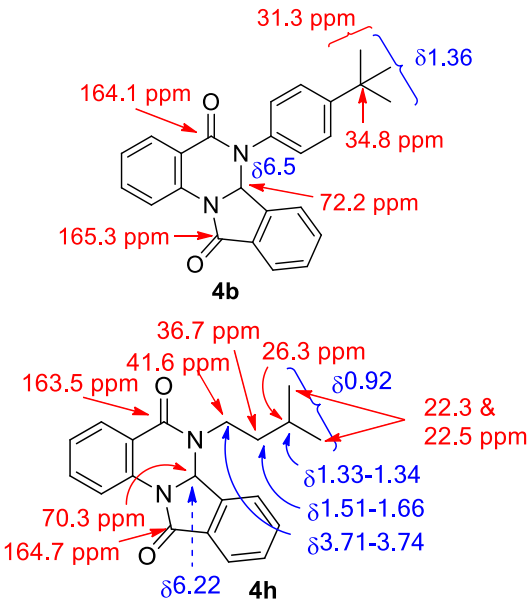


Fig. 2. Partial representation of ^{1}H (blue) and ^{13}C NMR (red) spectral data of compound **4b** and **4h**.

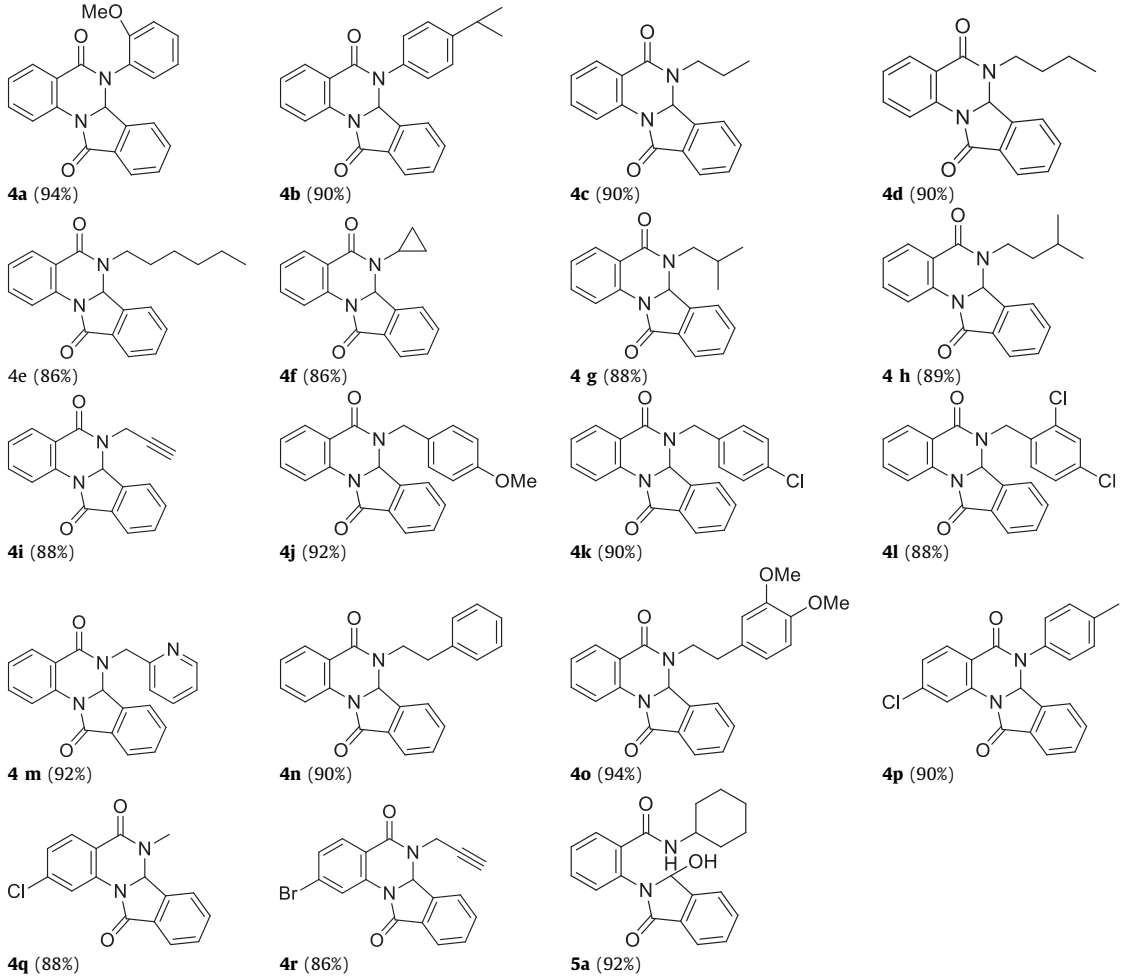
Table 2
Recyclability of the catalyst in the MCR of **1a, 2a** and **3a** to afford **4a** under the reaction condition of entry 5 of Table 1.

Cycle	Time (h)	Yield (%)
1st	8	94
2nd	8	94
3rd	8	92
4th	8	92
5th	8	92

2. Results and discussion

To establish the optimized green reaction conditions, the MCR of isatoic anhydride (**1a**), 2-methoxyaniline (**2a**) and 2-formylbenzoic acid (**3**) was performed under various conditions (Table 1). A number of catalysts including the resin bound Wang-SO_3H was screened for this purpose. The use of catalyst such as Amberlite IR120H, $NaHSO_3$–SiO_2, INDION 225H and PMA-SiO_2 (10% w/w each) in pure and demineralized water at 100 °C for 16 h afforded the desired product **4a** in low to moderate yield (entries 1–4, Table 1). However, a dramatic improvement in product yield was observed when the resin bound Wang-SO_3H was used (entry

Table 3
Green synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives **4** and related compounds **5** (Scheme 2).[a,b].

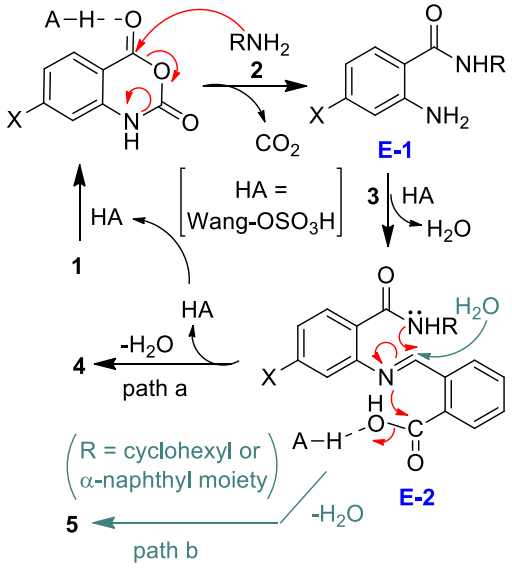


[a] Reaction conditions: isatoic anhydride **1** (1.0 mmol), amine **2** (1.0 mmol), 2-formylbenzoic acid **3** (1.1 mmol), and resin bound Wang-OSO_3H (10%w/w) in demineralized water (4 mL) at 100 °C for 8 h under open air.
[b] Figures in the bracket indicate%yield.

Table 4
The interaction of molecules **4j, 4k** and **6** with the SARS-CoV-2 N-terminal RNA binding domain.

Molecules	Estimated Total Energy (kcal/mol)	Interacting residues at binding site[a]
4j	−85.18	ARG42, THR44, GLN11, ASP16, PRO54
4k	−83.05	ASN28, ILE94, SER31, ILE105, ASN30, TRP5
6	−80.09	GLN11, ASP16, ARG42, LEU52

[a] The underlined residue was involved in H-bonding interaction.



Scheme 3. The proposed reaction mechanism for the MCR leading to formation of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives **4**.

5, Table 1). Indeed, the reaction proceeded much faster in this case and was completed within 6 h. While this catalyst was found to be effective in a number of other solvents e.g. PEG-400, PEG-200, ethylene glycol, EtOH, 1,4-dioxane and MeCN (entries 6–11) however the product yield was not comparable to that observed in case of water. The second best yield of **4a** (observed when PEG-400 was used) was considerably less than that obtained in water (entry 5 vs 6, Table 1). All these reactions were carried out using 10% w/w of catalyst. A decrease in catalyst loading to 5% w/w decreased the product yield to 85% whereas the product yield was dropped substantially when the catalyst was omitted (entry 10, Table 1). Similarly, the increase of catalyst loading to 15 or 20% w/w did not improve the product yield further. Overall, the condition of entry 5 of Table 1 was found to be optimum and therefore was used for further studies.

We then examined the recovery and reuse of the catalyst used i.e. Wang-OSO_3H in the synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivative **4a**. Accordingly, after completion of the reaction (the first cycle, Table 2) the reaction mixture was diluted with MeOH (100 mL) and the catalyst was recovered by simple filtration. The recovered catalyst was washed with MeOH (3 × 50 mL), water (10 mL) and acetone (10 mL) and dried under vacuum. The catalyst was then reused for several times (2nd, 3rd, 4th and 5th cycle, Table 2) without significant loss of activity as evident from the product yield.

We have demonstrated that the combination of resin bound Wang-OSO_3H and pure water could be an effective alternative for the synthesis of compound **4a** under green reaction conditions. To expand the generality and substrate scope of this methodology we employed a range of amines (**2**) in this MCR and the results are summarized in Table 3. Both aromatic (e.g. aniline derivatives) and aliphatic (e.g. alkyl and alkylaryl) amines were employed. The aliphatic amines may contain a linear or branched hydrocarbon or even a cyclopropyl ring. The use of propargyl amine and pyridin-2-ylmethanamine was also explored. The reaction proceeded well in all these cases affording the corresponding products in good yield (> 85% in most cases). The crude product obtained was purified by re-crystallization from EtOH in several cases particularly where product yield was > 90% though the column chromatography purification was used in rest of the cases. The isatoic anhydride containing Cl or Br substituent at C-7 position was also employed and found to be effective. Notably, the use of cyclohexylamine afforded the corresponding 2-(1–hydroxy-3-oxoisoindolin-2-yl)benzamide derivative **5a** (Table 3) instead of respective desired product. Both these compounds were found to be stable and could be isolated as well as characterized by spectral data. The fact that these compounds could not be converted to the corresponding isoindolo[2,1-*a*]quinazoline-5,11–dione derivative (when treated with Wang-OSO_3H in water at 100 °C separately) suggested the possibility of involvement of some different steps in these reactions. The unexpected formation of compound **5** could be due to the use of amines that are bulky in nature (see the mechanistic discussion later). Nevertheless, all the reactions were performed under open air and the methodology was free from the use of inert or anhydrous atmosphere thereby allowing the reaction to be performed in an open vessel. This is advantageous for the scale-up synthesis as the use of closed reaction vessel is associated with the potential risk of pressure development. Further, the use of inexpensive, safe and non-hazardous solvent water as a reaction media is another advantage of the current method. To assess the scale-up potential of this methodology the preparation of **4a** was undertaken in gram scale. Thus isatoic anhydride **1a** (1.63 g, 10 mmol), 2-methoxyaniline **2a** (1.23 g, 10 mmol) and 2-formylbenzoic acid **3** (1.65 g, 11 mmol) was reacted in the presence of resin bound Wang-OSO_3H (0.16 g, 10%w/w) in demineralized water (40 mL) under the conditions of entry 5 of Table 1 when the product **4a** was obtained almost in quantitative yield (98%).

All the isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives **4** synthesized were characterized by spectral (^{1}H and ^{13}C NMR and HRMS) data. The partial ^{1}H and ^{13}C NMR spectral data of two representative compounds e.g. **4b** and **4h** are presented in Fig 2. Two singlets at 1.36 and 6.5 δ in the ^{1}H NMR spectra was due to the *t*–butyl and C-6 proton of **4b** respectively whereas in case of **4h** a doublet at 0.92 δ accounting 6 protons was due to its two methyl groups and a singlet at 6.22 δ was due to its C-6 proton. Further, the ^{1}H NMR spectra of **4h** showed the presence of two multiplets at 1.33–1.34 and 1.51–1.66 δ due to the protons of >$CHCH_2$- group and another set of multiplets at 3.71–3.74 and 3.88–3.90 δ due to the two protons of -NCH_2- moiety. The two C=O groups of fused cyclic amide rings and the C-6 carbon appeared at 165.3 (5-membered ring), 164.1 (6-membered ring) and 72.2 ppm, respectively in the ^{13}CNMR spectra of **4b** whereas the *t*–butyl group appeared at 34.8 (the tertiary carbon) and 31.3 (three Me groups) ppm. Similarly, the two C=O groups and the C-6 carbon appeared at 164.7, 163.5 and 70.3 ppm, respectively in the ^{13}CNMR spectra of **4h** and the ^{13}C signals for the alkyl side chain could be presented as 41.6 (for NCH_2), 36.7 (for other CH_2), 26.3 (for -CH<), 22.3 (for one Me) and 22.5 (for another Me). In case of compound **5a** the presence of additional OH group was indicated by the HRMS data.

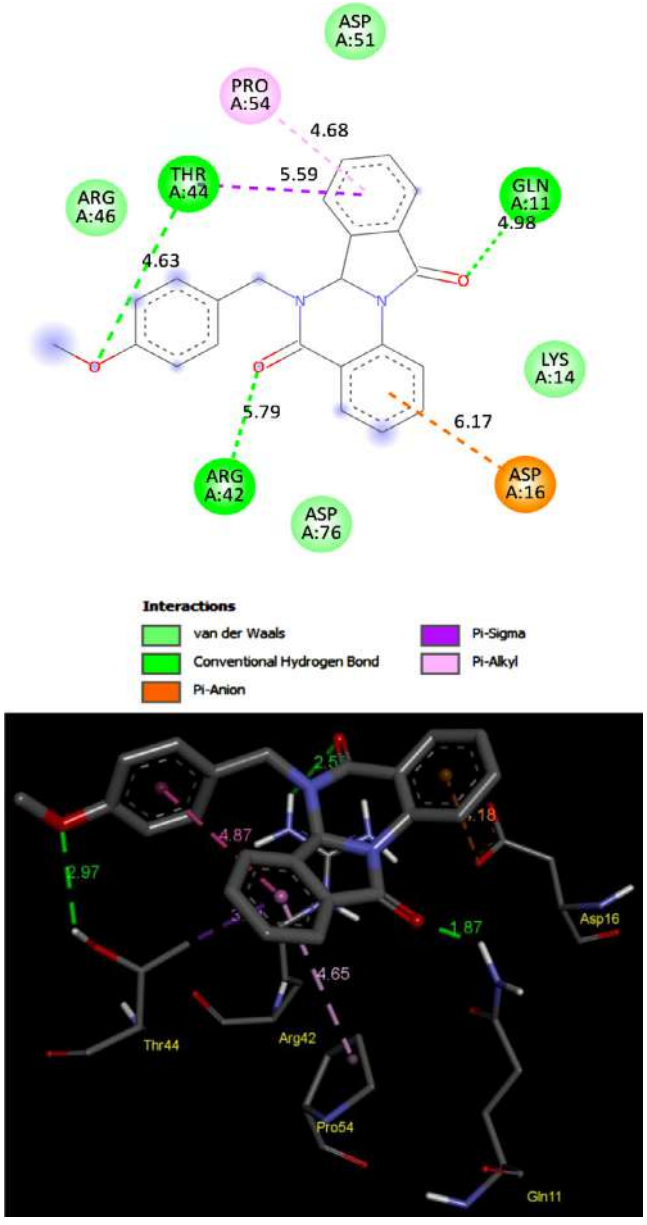


Fig. 3. 2D and 3D interaction diagram of SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (PDB: 6M3M) with compound **4j**.

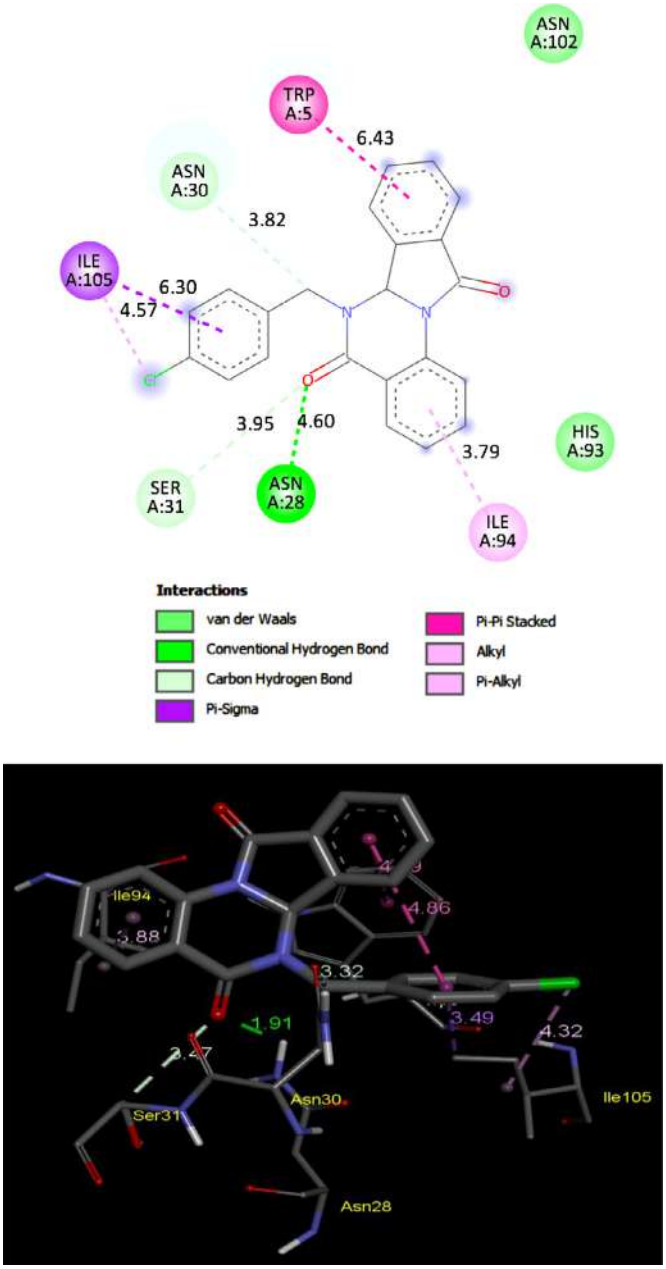
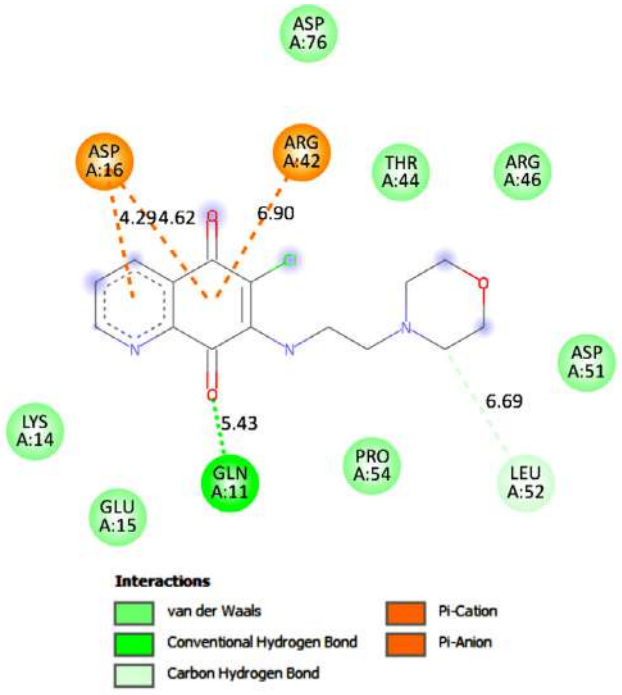


Fig. 4. 2D and 3D interaction diagram of SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (PDB: 6M3M) with compound **4k**.

Moreover, the two D_2O exchangeble protons appeared at 8.88 and 8.31 δ in the ^1H NMR spectra recorded in DMSO–d_6 (at 8.69 and 5.99 δ in $CDCl_3$) indicated the presence of CONH and OH group, respectively.

Mechanistically (Scheme 3), the reaction seems to proceed *via* the generation of two key intermediates in situ e.g. (i) **E-1** formed as a result of condensation of amine (**2**) with the isatoic anhydride (**1**) activated by the resin bound Wang-OSO_3H (HA) and (ii) the imine intermediate **E-2** formed *via* HA catalyzed condensation of **E-1** with 2-formylbenzoic acid **3**. The HA then facilitated an intramolecular concurrent cyclization where the azomethine moiety of **E-2** participated in the process. Thus with the subsequent involvement of the proximate carboxylic acid and the amide group the intermediate **E-2** afforded the desired product **4** (path a, Scheme 3). Notably, the participation of amide group in this step was restricted when the R group was chosen as a bulky cyclohexyl ring and the participation of water molecule present in a large volume was facilitated over the amide moiety to afford the unexpected product **5** (path b, Scheme 3). It is therefore possible that a different type of product can be obtained from the same MCR depending on the nature and type of amine employed.

Among the compounds synthesized **4j** and **4k** has been reported as potent inhibitors of TNF-α previously [1]. In our current effort these two compounds were selected for the docking studies *in silico*. The iGEMDOCK version 2.1 software [20] (a graphical automatic drug design system for docking, screening and analysis) being a program for computing ligand conformation and orientation relative to the active site of the protein was used for this purpose. The *in silico* docking studies were performed to evaluate the molecular interactions of compounds **4j** and **4k** along with the reference compound i.e. 6–chloro-7-((2-morpholinoethyl)amino)quinoline-5,8–dione **6** [21] with the SARS-CoV-2 nucleocapsid protein *N*-terminal RNA binding domain (PDB: 6M3M). The corresponding binding energies and the interacting



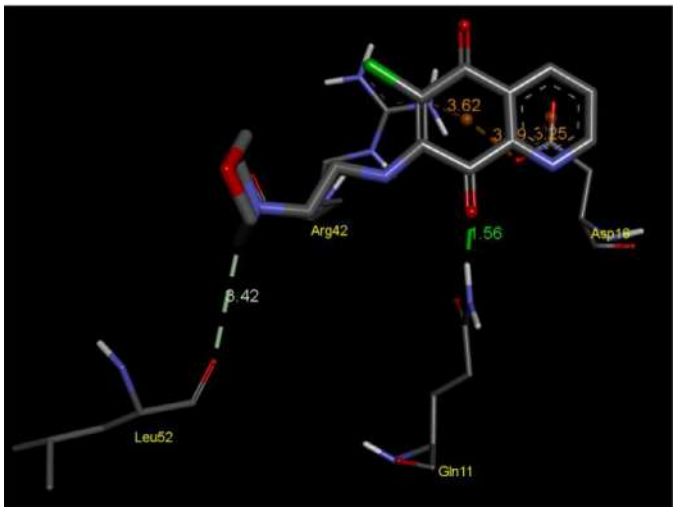


Fig. 5. 2D and 3D interaction diagram of SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (PDB: 6M3M) with compound **6**.

residues are listed in Table 4. Both the compounds i.e. **4j** and **4k** showed superior binding energies than the reference compound **6**. While all the molecules participated in the H-bonding interactions through the C=O group (Fig. 3-5), the highest number of such interactions was observed in case of **4j** that was reflected in its binding energy. Indeed, its OMe group formed a H-bond with THR44 in addition to two other H-bonds with GLN11 and ARG42 formed by its two C=O groups (Fig. 3). Besides, the molecule also participated in pi-sigma, pi-alkyl and pi-anion interactions with the residue THR44, PRO54 and ASP16, respectively. Thus the compound **4j** emerged as a potential ligand for SARS-CoV-2 that deserves further investigation.

3. Conclusions

In conclusion, for the first time the sulphonic acid-functionalized Wang resin (Wang-OSO_3H) was explored as a polymeric and recoverable acidic catalyst for the synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives under green conditions. Thus the Wang-OSO_3H catalyzed MCR of isatoic anhydride, 2-formylbenzoic acid and various amines in pure water afforded a range of desired product in good to excellent (86–94%) yield. Being free from the use of inert / anhydrous atmosphere the methodology can be performed under open air and is amenable for scale-up synthesis. The catalyst can be recovered and recycled for several times without significant loss of its catalytic activity. The unexpected formation of 2-(1–hydroxy-3-oxoisoindolin-2-yl)benzamide derivative was observed in one case depending on the nature and type of amine employed. This observation suggested the possibility of accessing a different type of product separately from the same MCR by varying the reactant amine. A plausible reaction mechanism for the current MCR is presented explaining the reason for formation of two different products. The *in silico* assessment suggested that the compound **4j** a known inhibitor of TNF-α could be a potential ligand for SARS-CoV-2. Indeed, the compound showed favorable binding energies and participated in H-bond interactions through its OMe and two C=O groups with the SARS-CoV-2 nucleocapsid protein *N*-terminal RNA binding domain. Overall, the current study not only demonstrated the effectiveness of Wang-OSO_3H as a catalyst for the green synthesis of isoindolo[2,1-*a*]quinazoline-5,11–dione derivatives but also suggested the potential utility of this class of compounds against COVID-19.

Credit author statement

G Dhananjaya, Rapolu Venkateshwarlu, Naresh Kumar Reddy Dinne, Avula Mahesh Kumar, and Ramamohan Mekala were involved in the preparation, isolation, purification and characterization of all the target compounds presented in the current manuscript.

Ravikumar Kapavarapu was involved in performing all the *in silico* studies.

Venkateswara Rao Anna and Manojit Pal were responsible conceptualization, coordination and overall supervision of the entire work presented in the submitted manuscript.

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131922.

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