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An efficient green approach for the synthesis of benzothiazole-linked pyranopyrazoles as promising pharmacological agents and docking studies

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Abstract

Benzothiazole-tethered pyranopyrazoles derivatives were prepared via environmentally favorable conditions, which included eco-friendly catalyst, ethanol −water solvent, one-pot reaction, and atom- and step-economy procedures. Excellent yield of the products was observed. Besides, all products were screened for their antimicrobial behavior. From the biological results, it was seen that most of the compounds possessed high to moderate antimicrobial properties. Compound **6a** gave prominent antimicrobial property followed by **6d**, **6l**, and **6n**. In addition, computer-aided studies of the active compounds were also conducted. In this, selected compounds were docked into the intercalation site of DNA of the DNA−gyrase complex. From these results, the highest binding energy of −10.1 kcal/mol was for **6a** against DNA−gyrase. This is the first eco-friendly synthetic method for the preparation of benzothiazole-pyranopyrazoles and the synthetic effort in this study may serve as a model for additional environmentally benign reactions. The biological results may prompt further studies related to antibiotic drugs.

1 | INTRODUCTION

The synthesis of biologically potent compounds usually involves a few routine and common benchmarks, but synthetic routes involving environmentally favorable strategies are far more critical because extra criteria related to health and impacts on Nature must also be included. The overarching perception of the 12 ideologies of environmental chemistry is to initiate the growth and application of eco-friendly reagents, which consequently will lead to reduced toxicity and pollution to the environment as well as to human health.[1] Mostly, in synthetic works, environmental threats occur because of the consumption of toxic metal catalysts, multi-step reactions, and use of hazardous solvents. To avoid the above conditions, we make use of eco-friendly reagents,[2,3] green solvents,[4] reusable catalysts, and biodegradable elements, control of multiple steps, and use of an iterative approach are attractive strategies in the area of synthetic research.[5–9] Besides, from the green chemistry point of

view, use of recyclable catalysts in multicomponent synthetic pathways plays an important role to avoid bulk usage of the catalyst and achieve economy. On the other hand, compared to the regularly used synthetic organic solvents, water-based solvents are desirable because they are eco-friendly in synthetic research. The prime nature of such solvents is that they can speed up the frequency of product formation.[10] Recently, many synthetic works have been carried out in the presence of aqueous media.[11–15]

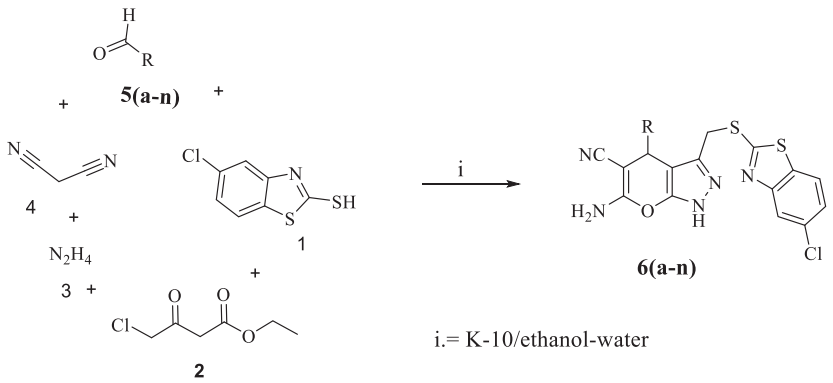
There is a metric established for the use of antibiotics by the World Health Organization called DDD (defined daily dose).[16,17] But the strength of this metric is doubtful in hospitalized humans because its measurement is based on human weight. In real cases, most health centers do not follow these metrics, and as a result pathogenic resistance is rising. Moreover, one of the reasons for the rise of microbial resistance is the inappropriate prescriptions in hospitals.[18] The relation between the inadequate usage of antibiotics and the rise in bacterial resiatance has been evidently noticed, resulting in increased mortality and costs.[19] Thus, in an epoch of antibiotic defiance, to discover effective and new antibiotics gets precedence.[20]

Sulfur-included benzo-fused moieties such as benzothiazoles display a broad range of biological properties, including antimicrobial,[21,22] antiviral,[23] antitumor,[24–26] and anti-HIV [27] activities. Besides, pyranopyrazole and their byproducts play an important role in biological organic research, because these compounds display antioxidant and anti-inflammatory properties,[28,29] act as antifungal agents,[30,31] and possess antibacterial.[32] and anticancer properties [33] There are many reports that a pyranopyrazole core and/or in combination with pyranopyrazole holds many synthetic defects. Some synthetic routes involve the use of metal catalysts, [34,35] while some others involve complicated processes. [36] Moreover, in the presence of a heavy catalyst like Fe-CaOx, Gangu and coworkers have reported a preparation method for such type of compounds.[37] Without the use of any solvent or catalyst, a few researchers have reported synthetic routes for pyranopyrazole derivatives.[38,39] In fact, some other synthetic reports also exist,[40,41] but all such methods have a few downsides. Based on all the above reports and our own experience in the field of organic synthesis,[42–45] we have undertaken in the current work the environmentally friendly synthesis of benzothiazole-fused pyranopyrazoles. Furthermore, antimicrobial activities of the compounds were studied along with computer-aided calculations.

2 | RESULTS AND DISCUSSION

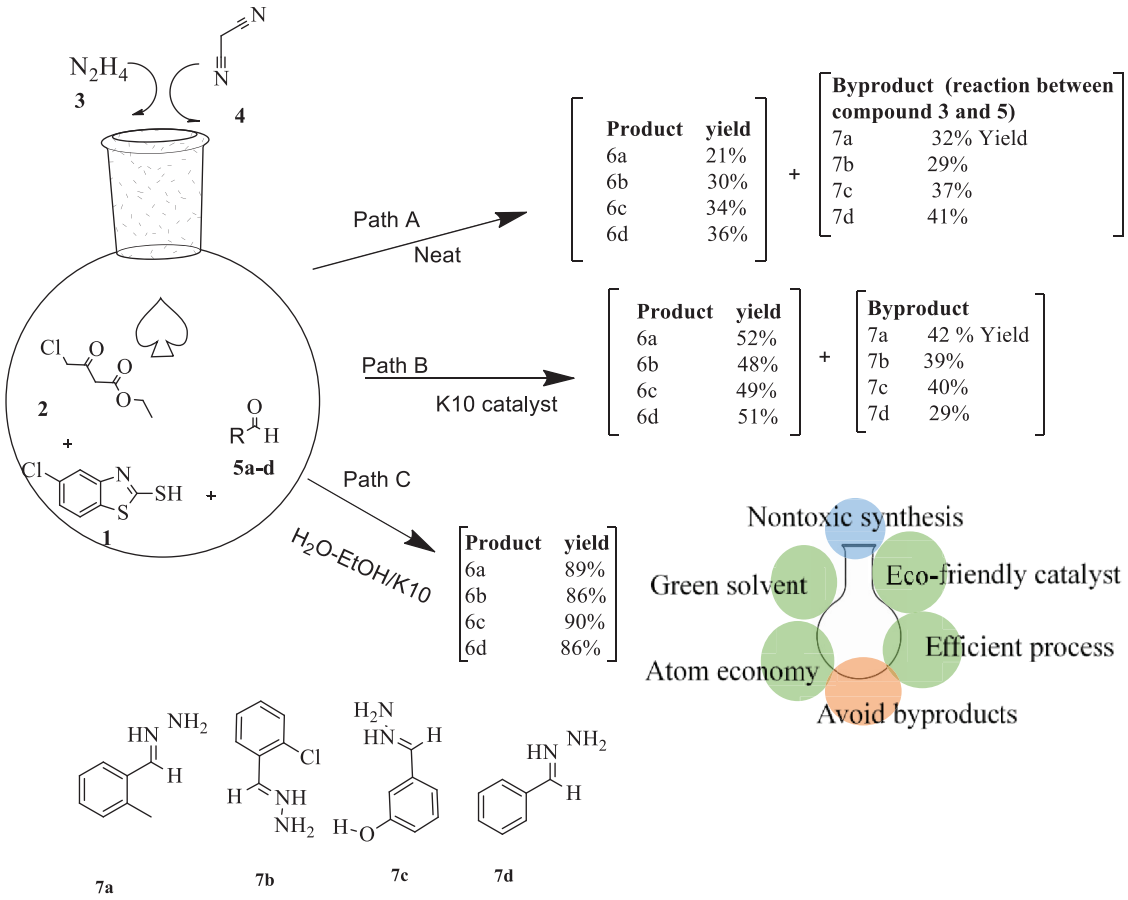
2.1 | Chemistry

The main goal was to prepare benzothiazole-fused pyranopyrazoles via an environmentally favorable synthetic method (Scheme 1). For this, we attempted various synthetic approaches. At first, we prepared only **6a**, **6b**, **6c**, and **6d** using different eco-friendly methods, which might lead to controlled reagent usage and cost minimization. Later, the rest of the compounds **6e–6n** were prepared by using the most efficient method. In this manner, initially a neat reaction was carried out to prepare the compounds **6a–6d** using their corresponding starting reactants. As a result, the products were formed successfully but only trace yields of the products were obtained (Path A, Scheme 2). The cause of the low yield might be the lack of solvent or catalyst. In this method, the corresponding side products **7a–7d** were also formed (Scheme 2). Further, to get better yields of the products as well as to maintain environmentally safe conditions,



R a = 2-$CH_3C_6H_4$ (Yield 89%), b = 2-ClC_6H_4 (86%), c = 3-OHC_6H_4 (90%), d = C_6H_5 (86%), e = 2-OHC_6H_4 (91%), f = 4-$OMeC_6H_4$ (90%), g = 4-FC_6H_4 (89%), h = 4-$NO_2C_6H_4$ (90%), i = 4-BrC_6H_4 (91%), j = 3-FC_6H_4 (90%), k = 4-MeC_6H_4 (88%), l = 2-$OMeC_6H_4$ (86%), m = 4-ClC_6H_4 (87%), n = 4-OHC_6H_4 (86%)

SCHEME 1 Preparation of benzothiazole-linked dihydropyranopyrazoles



SCHEME 2 Compounds **6a–6d**: production ways

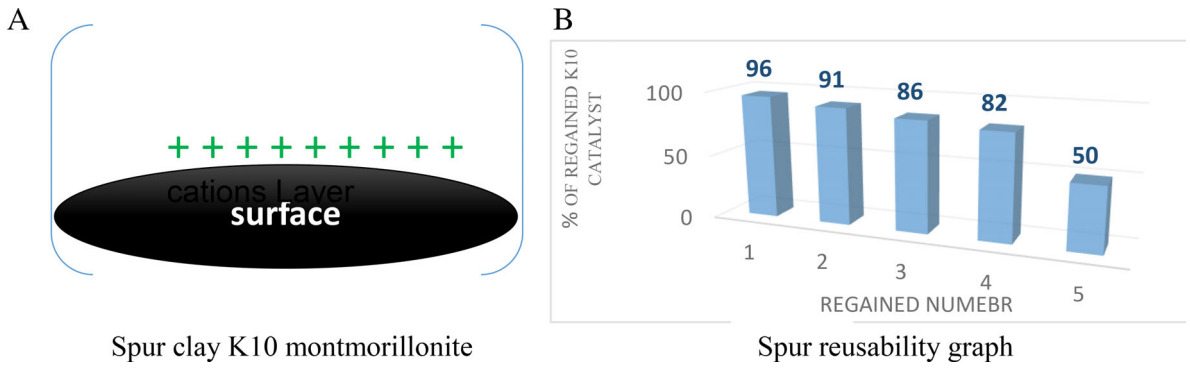


FIGURE 1 Catalyst details. (A) Spur clay K10 montmorillonite. (B) Spur reusability graph

we decided to use the montmorillonite K10 catalyst. Because, the K10 acid catalyst has such characteristics as eco-friendliness, reusability, nontoxicity, and simple work-up conditions, this catalyst belongs to the class of environmentally friendly mateerials (Figure 1A). When the K10 catalyst was inserted and the above neat reactions were carried out again (Path B, Scheme 2), the compound **6a** was formed with a yield of 52%, **6b** with 48%, **6c** with 49%, and **6d** with 51%. Here also, byproducts were formed.

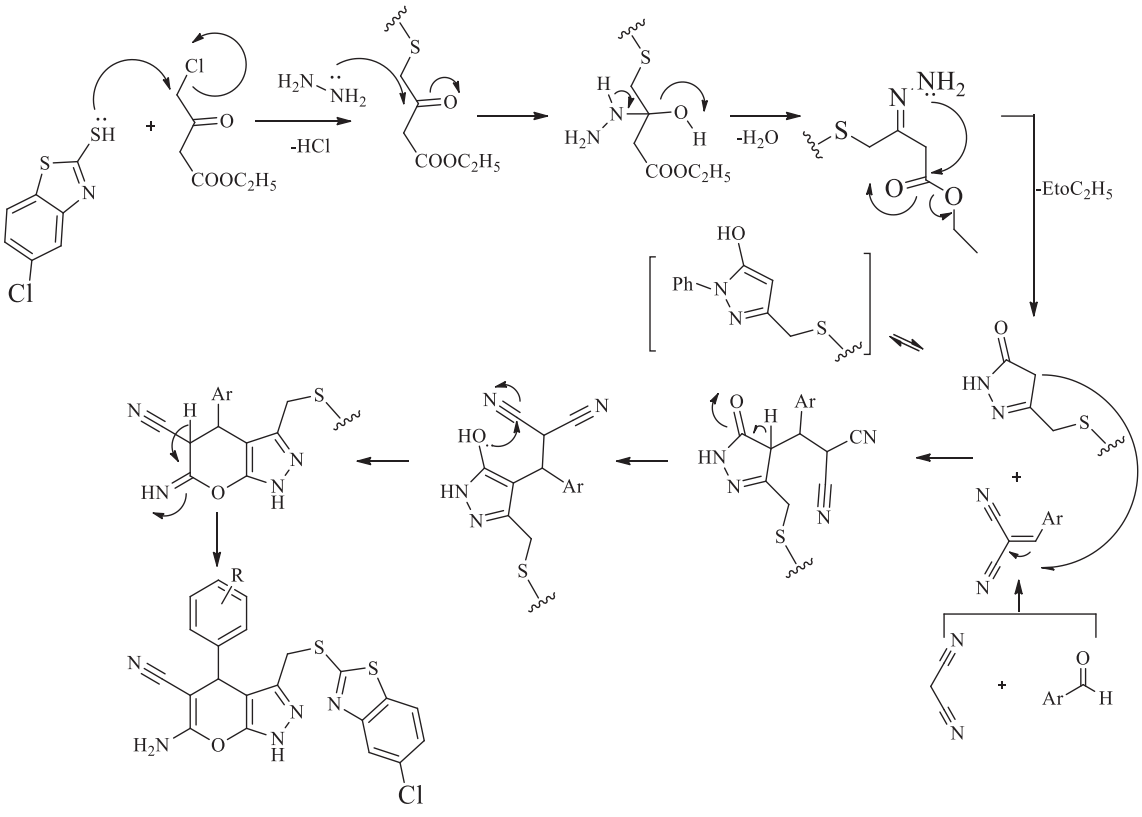
Even though the above two methods come under environmentally favorable approaches, they are not efficient due to the low yield. Generally, getting quantitative yield also comes under the environmentally friendly research category. This is because a high yield of the product leads to the minimization of chemical usage, controls repeat of the reaction, and avoids pollution during the repeat reaction, work-up, and so on. Keeping this strategy in mind, we decided to use an environmentally friendly, nontoxic, simple-to-handle solvent with no extra

cost. Water–ethanol solvent in the ratio 4:1 was taken, and it was added to the reaction mixture containing all the starting compounds of product **6a** including the K10 catalyst (Path C, Scheme 2). Consequently, **6a** was formed with 89% yield. By using the same method, the compounds **6b**, **6c**, and **6d** resulted with 86%, 90%, and 86% yield. That means outstanding results were observed using this method. Moreover, there were no byproducts formed in path C. The reason may be the presence of the solvent that will help mix the reactants clearly, and as a result, the yields were quantitative. Based on path C, the rest of the products **6e–6n** were prepared, resulting in high yields of the products. Interestingly, the K10 catalyst could be recycled up to five times and used for other reactions (Figure 1B). This was the additional advantage of this eco-friendly method. The possible way for the preparation of the target compounds is shown in Scheme 3.

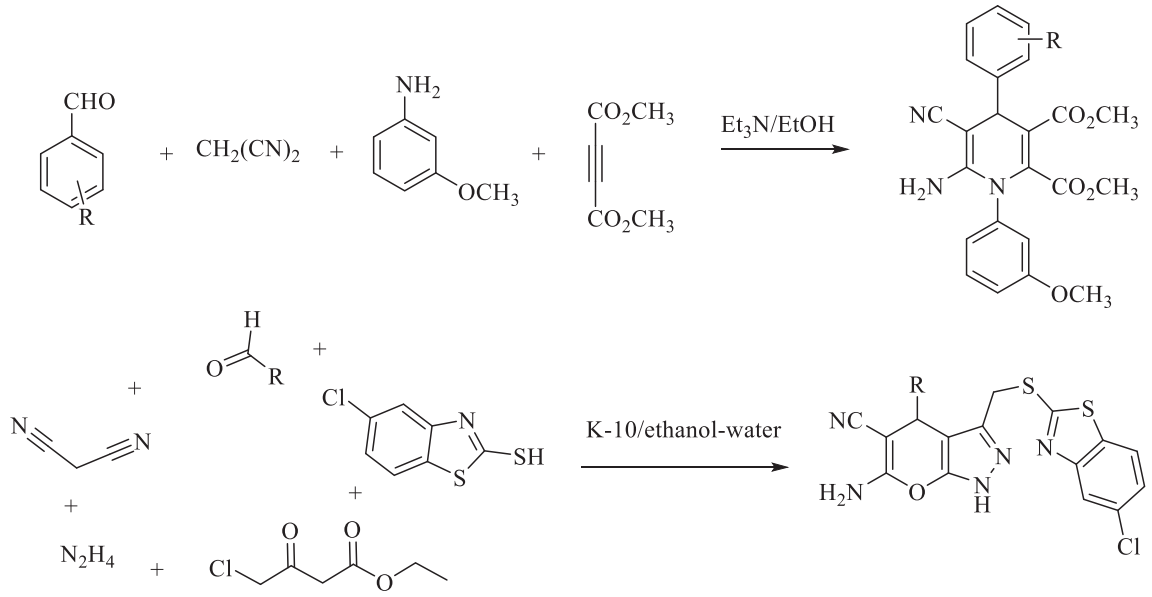
Previously, we had tried the four-component one-pot synthesis of dihydropyridine derivatives (Scheme 4)[46] under simple synthetic conditions, but obtained only low yields; and the synthetic methodology was not eco-friendly. From this point of view and based on the above results, a route involving PASE (pot, atom, step economy) and eco-friendliness could be achieved in this synthetic research. The final path had many advantages like ecological favorability, involvement of water as well as a water-miscible solvent, convenient work-up, and profitable product. In addition, K10 spur itself had eco-friendly behavior, was reusable, and played a vital role to get high yields.

2.2 | Biological discussion

The antimicrobial screening results of all synthesized compounds against four bacteria are tabulated in Table 1. All the antibacterial tests were carried out in two different concentrations. Ciprofloxacin was taken as the reference drug for antibacterial studies. From the antibacterial results, we were delighted to see that, except two compounds **6g** and **6h**, all the other compounds showed reliable toxicity on the four bacteria. The exceptional compounds were inactive towards Gram-negative bacteria such as *P. vulgaris* and *E. coli* and showed only trace antibacterial effects towards Gram-positive bacteria. In fact, all the active compounds delivered high to minimum antibacterial properties towards Gram-positive bacteria. Fascinatingly, the screened compounds showed strong opposition only to *S. aureus* bacteria. This means that these compounds (**6a–6n**) were more potent to destroy the Gram-positive microbes and can work as antibacterial agents. Among the antibacterial



SCHEME 3 Possible path for the formation of the target



SCHEME 4 Comparative schemes previous and current synthetic plans

TABLE 1 Bacterial and fungal killing nature of all synthesized compounds **6a–6n**

No.	Diameter of prevention (mm)											
	Bacteria								Fungi			
	GPB				GNB				*A. niger* (MTCC-1881)		*A. flavus* (MTCC-1884)	
	ATCC-19433 (*S. aureus*)		ATCC-6633 (*B. subtilis*)		ATCC-29213 (*P. vulgaris*)		ATCC-8739 (*E. coli*)					
	50 µg/well	100 µg/well	50 µg/well	100 µg/well	50 µg/well	100 µg/well	50 µg/well	100 µg/well	50 µg/well	100 µg/well	50 µg/well	100 µg/well
6a	44 ± 1	48 ± 3	38 ± 1	41 ± 3	32 ± 2	38 ± 1	27 ± 1	30 ± 2	35 ± 2	40 ± 2	28 ± 2	32 ± 2
6b	16 ± 2	21 ± 3	15 ± 1	21 ± 2	10 ± 2	15 ± 1	0	05 ± 1	14 ± 2	18 ± 1	08 ± 1	11 ± 1
6c	25 ± 3	31 ± 2	22 ± 1	26 ± 1	17 ± 2	23 ± 1	08 ± 3	12 ± 3	20 ± 2	25 ± 2	13 ± 3	17 ± 1
6d	42 ± 3	45 ± 2	36 ± 1	40 ± 1	30 ± 1	35 ± 2	25 ± 2	28 ± 1	33 ± 2	39 ± 3	26 ± 1	30 ± 1
6e	28 ± 1	33 ± 3	24 ± 3	29 ± 1	19 ± 3	25 ± 1	11 ± 1	16 ± 3	23 ± 1	27 ± 1	14 ± 1	19 ± 3
6f	31 ± 2	36 ± 2	27 ± 1	31 ± 1	21 ± 3	29 ± 1	15 ± 1	19 ± 3	24 ± 1	29 ± 1	16 ± 1	21 ± 1
6g	11 ± 3	16 ± 2	08 ± 1	13 ± 1	0	0	0	0	10 ± 3	13 ± 3	04 ± 1	06 ± 3
6h	09 ± 1	13 ± 2	06 ± 2	10 ± 1	0	0	0	0	06 ± 1	09 ± 1	03 ± 2	04 ± 1
6i	21 ± 2	28 ± 2	20 ± 1	24 ± 2	14 ± 2	19 ± 3	05 ± 2	09 ± 2	18 ± 2	22 ± 2	11 ± 1	16 ± 2
6j	14 ± 1	19 ± 2	13 ± 3	17 ± 2	09 ± 2	11 ± 2	0	04 ± 1	11 ± 1	15 ± 2	06 ± 1	09 ± 1
6k	34 ± 3	39 ± 1	29 ± 2	35 ± 2	24 ± 2	30 ± 2	17 ± 2	21 ± 1	27 ± 1	32 ± 1	21 ± 1	24 ± 3
6l	37 ± 1	41 ± 1	30 ± 1	36 ± 2	26 ± 1	31 ± 3	19 ± 2	23 ± 1	28 ± 1	33 ± 1	23 ± 2	25 ± 1
6m	20 ± 2	25 ± 1	18 ± 2	22 ± 3	13 ± 1	17 ± 2	03 ± 1	07 ± 1	16 ± 1	20 ± 3	10 ± 2	13 ± 2
6n	40 ± 2	44 ± 1	32 ± 2	38 ± 3	29 ± 1	33 ± 3	21 ± 2	25 ± 2	30 ± 2	36 ± 1	25 ± 2	29 ± 2
Ref	45 ± 2	49 ± 1	40 ± 2	43 ± 1	35 ± 1	39 ± 2	31 ± 1	33 ± 2	37 ± 1	41 ± 1	30 ± 2	34 ± 1
*	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: *, control dimethyl sulfoxide; GNB, gram-negative bacteria; GPB, gram-positive bacteria; Ref, Ciprofloxacin or Ketoconazole.

compounds, the highest antibacterial activity was observed in the case of compound **6a** towards four bacteria in all two test concentrations shown in Table 1. In addition, compounds **6d**, **6l**, and **6n** had the next leading effect on germs, while the compounds **6k** and **6f** displayed moderate antibacterial action.

Table 1 also shows the antifungal test results of the synthesized compounds on two fungi, namely *A. niger* and *A. flavus*. The antifungal examination was done in 50 and 100 micrograms per well concentrations, which is enough to detect prominent antifungal compounds. In these experiments, Ketoconazole was used as the standard drug. Compared to the reference drug, compounds **6a–6n** exhibited high to minimal antifungal effects on the two fungal strains. Moreover, all compounds displayed high antifungal activity towards *A. niger* only. Besides, molecule **6a** was found to be more fungal resistant than the other molecules, while the compounds **6d**, **6f**, **6k**, **6l**, and **6n** displayed good to moderate antifungal properties. On the other hand, the remaining molecules showed low to minimum toxicity towards the fungi.

2.3 | MIC (MBC/MFC) results

The minimum inhibitory concentrations (MICs) as well as the minimum bactericidal and fungicidal concentrations (MBC and MFC) of compounds **6a**, **6d**, **6n**, and **6l** are tabulated in Table 2. It is observed that **6a** delivered the minimum bacterial and fungal concentrations

TABLE 2 MIC (MBC/MFC) of targets **6a**, **6d**, **6n**, and **6l**

Samples	MIC (MBC/MFC)					
	S. aureus	***B. subtilis***	***P. vulgaris***	***E. coli***	***A. niger***	***A. flavus***
6a	25 (50)	50 (100)	100 (>200)	25 (100)	25 (50)	50 (200)
6d	50 (100)	100 (>200)	50 (>200)	100 (>200)	100 (200)	50 (>200)
6n	25 (100)	50 (200)	25 (200)	50 (200)	50 (200)	25 (100)
6l	50 (200)	50 (>200)	25 (100)	50 (200)	25 (100)	100 (>200)
Ref[a]	6.25	12.5	12.5	12.5	-	-
Ref[b]	-	-	-	-	12.5	12.5

[a]Ref = Ciprofloxacin.
[b]Ref = Ketoconazole.

TABLE 3 Docking scores of the docked compounds

Compunds	BA (kcal/mol)	R
6a	−10.1	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E),Ser-84(A), Arg-122(C), Asp-437(B), Arg-458(B), Asn-476(B), Glu-477(B)
6d	−9.9	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E),Ser-84(A), Arg-122(C), Asp-437(B), Arg-458(B), Asn-476(B), Glu-477(B)
6f	−9.1	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E), Arg-122(C), Asp-437(B), Arg-458(B), Glu-477(B), Asn-475(B), Asn-476(B)
6g	−8.7	Thy-8(F), Gua-2009(F), Cyt-2012(E), Ade-2013(E), Thy-2014(E), Arg-122(C), Asp-437(B), Arg-458(B), Gly-459(B), Lys-460(B), Leu-462(B), Glu-477(B), Asn-475(B), Asn-476(B)
6h	−8.6	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E), Arg-122(C), Asp-437(B), Arg-458(B), Gly-459 (B), Asn-474(B), Asn-476(B)
6k	−9.4	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E), Arg-122(C), Asp-437(B), Arg-458(B), Gly-459 (B), Asn-476(B), Glu-477(B)
6l	−9.5	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E), Ser-84(A), Arg-122(C), Asp-437(B), Arg-458(B), Gly-459 (B), Asn-476(B), Glu-477(B)
6n	−9.9	Thy-8(F), Gua-2009(F), Gua-2010 (F), Cyt-2011(E), Cyt-2012(E), Ade-2013(E), Ser-84(A), Arg-122(C), Asp-437(B), Arg-458(B), Gly-459 (B), Asn-476(B), Glu-477(B)

Abbreviations: BA, binding affinity; R, residues.

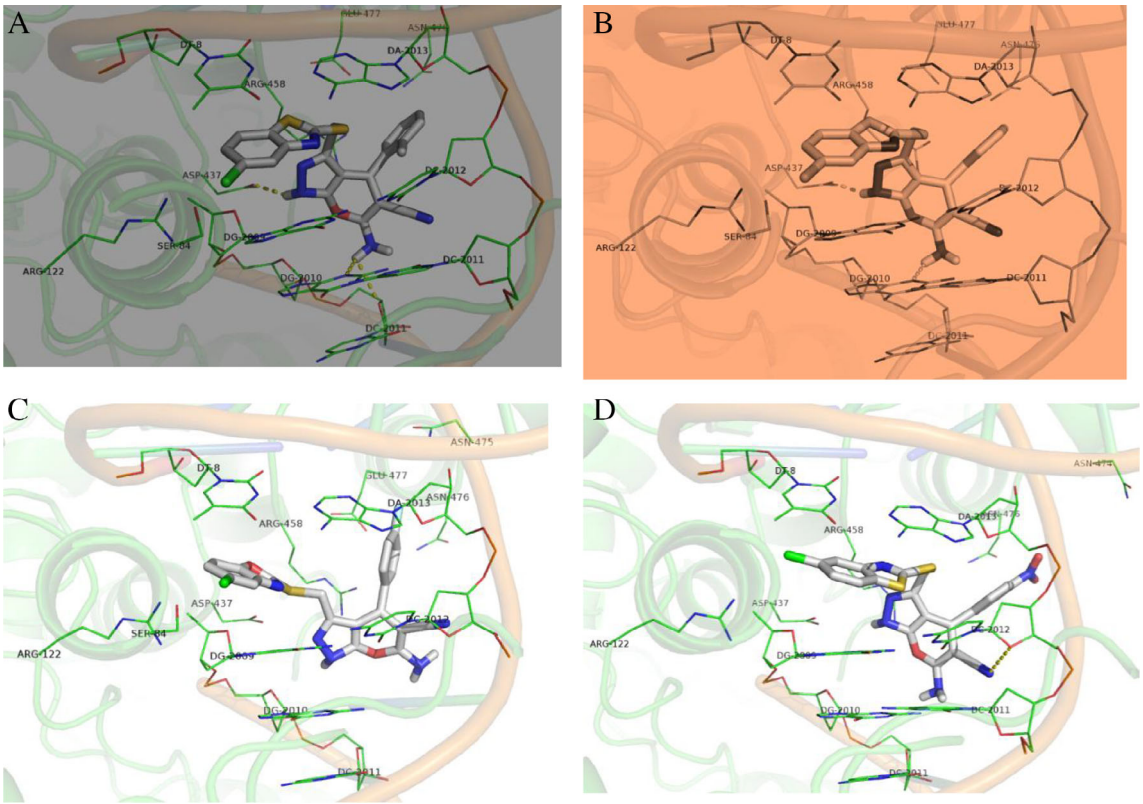


FIGURE 2 Docking of compounds **6a**, **6d**, **6g**, and **6h**. They were docked at the DNA–gyrase cleavage complex of *S. aureus* (PDB_ID:5CDQ). Inhibitor fragments are shown by white sticks and the DNA side chains and amino acid side chains are shown by lines

compared to standard drug. Its MBC and MFC were equal to twice the MIC against the two bacteria *S. aureus*, *B. subtilis* and the fungus *A. niger*. In addition, compound **6d** had MBC and MFC values twice the MIC against one bacterium and one fungus only. In fact, the remaining compounds had their MBC and MFC values greater than twice the MIC values.

2.4 | Molecular docking studies analysis

Table 3 shows the docking molecules' binding energy towards the DNA–gyrase cleavage of the complex *S. aureus* binding site enclosed by the protein residues, which were analyzed using molecular docking studies. The binding affinity of the molecule shows strong interaction energies with the DNA active site, and the results are shown in Figure 2 and Table 3.

According to Table 3, the molecules were docked into the intercalation location of DNA of the DNA–gyrase complex. The molecule bound to the DNA was stabilized by hydrogen bonding, hydrophobic, and π–π interactions. In all the eight molecules, the side chain 5-chlorobenazothiazole ring was stabilized by the thymine ring (DT-8) and guanine (DG2009) of the F chain with π–π interactions. The 1,4-dihydropyranopyrazole core containing NH forms a stable hydrogen bond with the side chain carboxylic oxygen of ASP-437 of the B chain, which was observed in active molecules **6a**, **6d**, **6l**, and **6n**. NH_2 forms a hydrogen bond with the side-chain ring nitrogen of F chain guanine (DG2010), as observed in **6a**, **6d**, **6k**, and **6n** molecules. The phenyl ring of the molecule **6d**, 2-methyl phenyl of **6a**, and 4-hydroxy phenyl of **6n**, substituted on 1,4-dihydropyranopyrazole ring were stabilized by the B chain amino acid residues Asn-476, Arg-458, and Glu-477. The molecules **6h** and **6g** with the electron-withdrawing groups $-NO_2$ and –F on the phenyl ring and –OMe group in **6f** are stabilized by only Asn-476. The loss of the hydrogen bond with Asp-437 observed in molecules **6g** and **6h** may cause the decrease in the activity of these molecules. The interaction of DNA bases and the amino acid side-chain proteins with active **6a** and **6d** molecules and the less active molecules **6g** and **6h** is also shown in Figure 2 and Figure S1.

3 | CONCLUSION

In this study, a series of benzothiazole-included pyranopyrazoles were designed, synthesized, and screened

for their antimicrobial activities. The synthetic strategy in this research involved environmentally favorable conditions only. All the compounds were formed with good yields. In addition, antimicrobial test results showed that, except two compounds, all the other compounds displayed reliable antimicrobial effect towards bacteria and fungi when compared with standard drugs. In fact, compound **6a** showed high antimicrobial property, followed by **6d**, **6l**, and **6n.** Besides, molecular docking studies of compounds were conducted at the intercalation location of DNA of the DNA–gyrase complex. On the basis of computer-aided study results, the highest binding energy of −10.1 kcal/mol was shown by **6a** against DNA–gyrase.

4 | EXPERIMENTAL

4.1 | General

All the initial compounds, reagents, and solvents were commercially available. Melting points were verified by a micro melting point device and were uncorrected. Tetramethylsilane (TMS) was used as the internal standard ($\delta = 0$) for ^{1}H NMR. $CDCl_3$/$CDCl_3$ + DMSO were used for ^{13}C NMR. $CDCl_3$/DMSO ($\delta = 77.27$) was used as internal standard. For ^{1}H NMR, 300 MHz and for ^{13}C NMR 75 MHz were used. Carbon NMR spectra were obtained with complete proton decoupling. Low-resolution MS and HRMS data were obtained using ES ionization.[47-50]

4.1.1 | Procedure for the synthesis of 6a, 6b, 6c, and 6d

Path A: The five starting reagents, 5-chlorobenzo[d]thiazole-2-thiol (**1**, 1 mmol), ethyl 4-chloro-3-oxobutanoate (**2**, 1 mmol), hydrazine (**3**, 1 mmol), malononitrile (**4**, 1 mmol), and 2-methylbenzaldehyde (**5a**, 1 mmol) were taken in a round-bottom flask and the reaction was allowed to proceed at 60° under inert atmosphere for 5–7 h. After the completion of reaction, as checked by TLC, the product **6a** and the side product **7a** were isolated using chromatography. For this, ethyl acetate–hexane solvent mixture was used as the eluent. Similar procedures were followed to prepare **6b–6d**.

Path B: The same reaction mentioned above was carried out in the presence of the green montmorillonite K10 catalyst (0.5% by mass to **5a**) under same conditions. The compound **6a** and its byproduct resulted, which were isolated. Likewise, **6b**, **6c**, and **6d** were obtained.

4.1.2 | Preparation of targets 6a–6n

Path C: To all starting compounds of product **6a**, 5 mL of the solvent water–ethanol (4:1) was added, followed by the same volume of catalyst mentioned in Path B. After TLC check, the reaction mixture was filtered through a funnel containing cotton, and filtrate was evaporated using a rotary evaporator. The resulting solid product **6a** was recrystallized from methanol. The catalyst-containing cotton was dipped into ethyl acetate solvent. Consequently, the catalyst settled down at the bottom. The solvent was then decanted and the catalyst dried in an oven at 50°. The recovered clay was reused for further reactions. Similarly, the other targets **6b–6n** were synthesized.

Spectral data

6-Amino-3-(((5-chlorobenzo[d]thiazol-2-yl)thio)methyl)-4-(*o*-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6a**): Light yellow powder; yield 89%; m.p. 216°C–218°C; IR (KBr) (cm^{-1}): 3438, 3339 (NH_2), 2243 (C≡N), 1664 (C=N) 1639 (C=C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.32 (s, 3H, CH_3), 3.59 (s, 2H, CH_2), 4.53 (s, 1H, CH), 7.27–7.74 (m, 7H, Ar-H), 8.61 (br, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5 (amine attached C), 162.3 (N=C-S), 156.4 (O-C-NH), 152.3, 141.5, 134.9, 133.5, 131.2, 130.4, 128.6, 126.3, 124.1, 123.4, 122.2, 121.6, 121.1, 119.3, 111.3 (CN), 57.2 (C-CN), 34.1 (CH), 28.5 (CH_2), 17.3 (CH_3) ppm; HRMS: *m/z* calcd for $C_{22}H_{17}ClN_5OS_2$ $(M + H)^+$ 466.0563; Found 466.0560.

6-Amino-3-(((5-chlorobenzo[d]thiazol-2-yl)thio)methyl)-4-(2-chlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6b**) Light yellow powder; yield 86%; m.p. 183°C–185°C; IR (KBr) (cm^{-1}): 3440, 3341 (NH_2), 2239 (C≡N), 1662 (C=N) 1644 (C=C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.66 (s, 2H, CH_2), 4.54 (s, 1H, CH), 7.15–7.79 (m, 7H, Ar-H), 8.68 (br, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 168.4 (amine attached C), 160.9 (N=C-S), 155.6 (O-C-NH), 152.3, 142.6, 136.1, 134.5, 132.1, 129.3, 128.3, 126.5, 124.1, 123.2, 122.3, 121.1, 120.6, 119.5110.5 (CN), 57.2 (C-CN), 36.5 (CH), 31.0 (CH_2). ppm; HRMS: *m/z* calcd for $C_{21}H_{14}Cl_2N_5OS_2$ $(M + H)^+$ 486.0017; Found 486.0015.

6-Amino-3-(((5-chlorobenzo[d]thiazol-2-yl)thio)methyl)-4-(3-hydroxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6c**) Yellow powder; yield 90%; m.p. 205°C–207°C; IR (KBr) (cm^{-1}): 3447, 3329 (NH_2), 2234 (C≡N), 1676 (C=N) 1643 (C=C); ^{1}H NMR ($CDCl_3$): δ 3.72 (s, 2H, CH_2), 4.54 (s, 1H, CH), 7.26–7.74 (m, 7H, Ar-H), 8.51 (br, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5 (amine attached C), 160.8 (N=C-S), 155.2 (O-C-NH), 152.3, 142.6, 136.2, 135.4, 134.2, 133.2, 131.8, 128.4, 127.2, 126.5, 124.1, 122.2, 120.1, 119.4, 111.3 (CN), 56.3

(C-CN), 34.3 (CH), 29.5 (CH_2). ppm; HRMS: *m/z* calcd for $C_{21}H_{15}ClN_5O_2S_2$ $(M + H)^+$ 468.0356; Found 468.0354.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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REFERENCES

[1] P. T. Anastas, in *Green Chemistry: Theory and Practice* (Eds: P. T. Anastas, J. C. Warner), Oxford University Press, New York **1998**.
[2] P. Tundo, M. Selva, *Acc. Chem. Res.* **2002**, *35*, 706.
[3] X. Liu, S. Li, Y. Liu, Y. Cao, *Chin. J. Catal.* **2015**, *36*, 1461.
[4] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.* **2015**, *18*, 288.
[5] R. A. Sheldon, I. Arends, G. J. Ten Brink, A. Dijksman, *Acc. Chem. Res.* **2002**, *35*, 774.
[6] M. R. Guda, S. Gundala, P. Venkatapuram, P. Adivireddy, *Arab. J. Chem.* **2014**, *7*, 947.
[7] R. S. Boethling, E. Sommer, D. DiFiore, *Chem. Rev.* **2007**, *107*, 2207.
[8] R. A. Sheldon, C. R. Acad, *Sci. Ser. IIc Chim.* **2000**, *3*, 541.
[9] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301.
[10] M. Y. Han, J. Lin, W. Li, W. Y. Luan, P. L. Mai, Y. Zhang, *Green Chem.* **2018**, *20*, 1228.
[11] D. C. Rideout, R. Breslow, *J, Am. Chem. Soc.* **1980**, *102*, 7816.
[12] V. Luque-Agudo, M. V. Gil, E. Roman, J. A. Serrano, *Green Chem.* **2016**, *18*, 3844.
[13] D. Paprocki, M. Wilk, A. Madej, P. Walde, R. Ostaszewski, *Environ. Chem. Lett.* **2019**, *17*, 1011.
[14] X. Zhang, L. Yuan, F. Liang, D. An, Z. Chen, D. Feng, M. Xian, *Environ. Chem. Lett.* **2019**, *18*, 1.
[15] N. Azizi, M. Alipour, *Environ. Chem. Lett.* **2018**, *16*, 1415.
[16] O. M. Ibrahim, R. E. Polk, *Infect. Dis. Clin. North. Am.* **2014**, *28*, 195.
[17] S. Grau, G. Bou, E. Fondevilla, J. Nicolás, M. Rodríguez-Maresca, L. Martínez-Martínez, *Enferm. Infecc. Microbiol. Clin.* **2013**, *31*, 16.
[18] J. Bielicki, R. Lundin, S. Patel, S. Paulus, *Pediatr. Infect. Dis. J.* **2015**, *34*, 311.
[19] B. Amadeo, P. Zarb, A. Muller, N. Drapier, V. Vankerckhoven, A. M. Rogues, P. Davey, H. Goossens, *J. Antimicrob. Chemother.* **2010**, *65*, 2247.
[20] Antimicrobial Resistance, *Global Report on Surveillance*, Wolrd Health Organization, Switzerland **2014**.
[21] S. P. Vikas, N. B. Bhushan, D. G. Vinod, R. P. Kiran, S. P. Vikas, G. U. Prashant, N. Sekar, *Arab. J. Chem.* **2016**, *9*, s1125.
[22] A.-T. Mahmoud, Y. A. Al-Soud, A. Mahmud, K. Safaa, *Arab. J. Chem.* **2016**, *9*, S926.
[23] M. A. El-Sherbeny, *Arzneimittelforschung* **2000**, *50*, 848.
[24] T. D. Bradshaw, M. S. Chua, H. L. Browne, V. Trapani, E. A. Sausville, M. F. Stevens, *Br. J. Cancer* **2002**, *86*, 1348.
[25] I. Hutchinson, S. A. Jennings, B. R. Vishnuvajjala, A. D. Westwell, M. F. Stevens, *J. Med. Chem.* **2002**, *45*, 744.
[26] V. Bénéteau, T. Besson, J. Guillard, S. Léonce, B. Pfeiffer, *Eur. J. Med. Chem.* **1999**, *34*, 1053.
[27] L. Racane, V. Tralić-Kulenović, L. Fišer-Jakić, W. D. Boykin, G. Karminski-Zamola, *Heterocycles* **2001**, *55*, 2085.
[28] A. Kumar, P. Lohan, D. K. Aneja, G. K. Gupta, D. Kaushika, O. Prakasha, *Eur. J. Med. Chem.* **2012**, *50*, 81.
[29] S. C. Kuo, L. J. Huang, H. Nakamura, *J. Med. Chem.* **1984**, *27*, 539.
[30] P. W. Smith, S. L. Sollis, P. D. Howes, P. C. Cherry, I. D. Starkey, K. N. Cobley, H. Weston, J. Scicinski, A. Merritt, A. Whittington, P. Wyatt, *J. Med. Chem.* **1998**, *41*, 787.
[31] M. Kidwai, S. Saxena, M. K. Rahman Khan, S. S. Thukral, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4295.
[32] S. R. Mandha, S. Siliveri, M. Alla, V. R. Bommena, M. R. Bommineni, S. Balasubramanian, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5272.
[33] S. A. Patil, J. Wang, X. S. Li, J. Chen, T. S. Jones, A. H. Ahmed, R. Patil, W. L. Seibel, W. Li, D. D. Miller, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4458.
[34] M. Behrooz, S. S. Ashrafi, *RSC Adv.* **2014**, *81*, 42873.
[35] R. S. Aliabadi, N. O. Mahmoodi, *RSC Adv.* **2016**, *6*, 85877.
[36] A. Javid, A. Khojastehnezhad, H. Eshghi, F. Moeinpour, F. F. Bamoharram, J. Ebrahimi, *Org. Prep. Proced. Int.* **2016**, *48*, 377.
[37] K. K. Gangu, S. Maddila, S. N. Maddila, S. B. Jonnalagadda, *RSC Adv.* **2017**, *7*, 423.
[38] M. Koohshari, M. Dabiri, P. Salehi, *RSC Adv.* **2014**, *4*, 10669.
[39] B. P. Tripathi, A. Mishra, P. Rai, Y. K. Pandey, M. Srivastava, S. Yadav, J. Singh, J. Singh, *N. Journal of Chem.* **2017**, *41*, 11148.
[40] M. Bihani, P. P. Bora, G. Bez, H. Askari, *ACS Sustainable Chem. Eng.* **2013**, *1*, 440.
[41] J. B. Gujar, M. A. Chaudhari, D. S. Kawade, M. S. Shingare, *Tetrahedron Lett.* **2014**, *29*, 6030.
[42] G. M. Reddy, J. R. Garcia, G. Yuvaraja, M. V. Subbiah, J.-C. Wen, *J. Heterocycl. Chem.* **2020**, *57*, 2288.
[43] G. M. Reddy, D. Y. Chen, V. S. Munagapati, L. Jianyou, J. C. Wen, *J. Heterocyclic. Chem.* **2019**, *56*, 1806.
[44] V. H. Reddy, A. K. Kumari, G. M. Reddy, Y. V. R. Reddy, J. R. Garcia, G. V. Zyryanov, N. B. Reddy, A. Rammohan, *Chem. Heterocycl. Compd.* **2019**, *55*, 60.
[45] A. Rammohan, G. M. Reddy, J. R. Garcia, G. V. Zyryanov, G. Sravya, N. B. Reddy, G. Yuvaraja, *J. Heterocyclic. Chem.* **2019**, *56*, 470.
[46] G. M. Reddy, J. R. Garcia, N. B. Reddy, G. V. Zyryanov, G. Yuvaraja, *J. Heterocyclic. Chem.* **2019**, *56*, 845.
[47] G. M. Reddy, A. Camilo Jr., *Sustain. Chem. Pharm.* **2020**, *17*, 100303.
[48] O. Trott, A. J. Olson, *J. Comput. Chem.* **2010**, *31*, 455.

[49] G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, *J. Comp. Chemput.* **2009**, *30*, 2785.

[50] P. F. Chan, V. Srikannathasan, J. Huang, H. Cui, A. P. Fosberry, M. Gu, M. M. Hann, M. Hibbs, P. Homes, K. Ingraham, J. Pizzollo, C. Shen, A. J. Shillings, C. E. Spitzfaden, R. Tanner, A. J. Theobald, R. A. Stavenger, B. D. Bax, M. N. Gwynn, *Nat. Commun.* **2015**, *6*, 10048.

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