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RESEARCH ARTICLE

ONE POT GREEN SYNTHESIS OF BIOLOGICAL POTENT THIAZOLOPYRANS AND DOCKING AGAINST HUMAN PANCREATIC LIPASE RELATED PROTEIN 1 RECEPTORS

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ABSTRACT

A one-pot practical, efficient, and environmentally benign multi-component synthesis of thiazolopyrans using copper nanoparticles in ionic liquid has been developed. The synthesis was achieved via a three component reaction of an aldehyde, cyanoethyl acetate and thiazolidine-2, 4-dione. Further, docking study of thiazolopyrans on human pancreatic lipase related protein 1 receptor co-crystallized using iGEMDock was carried out. The intermolecular hydrogen bonding interaction of the best-fit ligands were found to be associated with His 449, Tyr 473, Cys 289 and Gln 286 amino acid residue at the receptor active site. Compound 4e forms hydrogen bonding with His 449 and Tyr 473 amino acid and gives the minimum energy in the docking result.

INTRODUCTION

In the present scenario, trans-disciplinary research addresses the most pressing societal problems. Over the past decades, multicomponent reactions (MCRs) have proved to be very powerful and efficient bond-forming tools in organic, combinatorial and medicinal chemistry in the context of green chemistry. The MCRs are very flexible, atom economic in nature, and proceed through a sequence of reaction equilibria, yielding the target product.

Along with other reaction parameters, the nature of the catalyst plays a significant role in determining yield, selectivity and general applicability. Thus, development of an inexpensive, mild, reusable and general catalyst for MCRs remains an issue of interest. [1-5] As a part of our continued interest in catalysis by metal nanoparticles, we have previously used Cu NPs in ionic liquid as reusable catalyst for carbon–sulphur, carbon-nitrogen and carbon–carbon bond forming reactions.

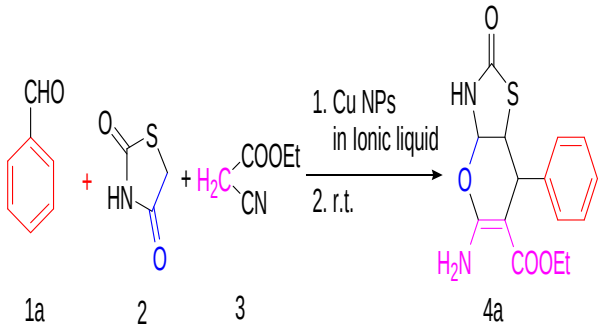
Recently, we found excellent selectivity of Cu NPs in ionic liquid for a MCR leading to highly substituted pyranothiazole derivatives in high yields without the formation of any by-products. The advantages of using Cu NPs in ionic liquid are: easy to synthesize at room temperature from readily available and inexpensive materials, stability at elevated temperatures, and non-volatile in nature. Besides the above mentioned characteristics, higher reactivity and excellent selectivity of the Cu NPs in ionic liquid prompted us to explore its full potential in other MCRs leading to products with practically important biological, pharmacological, and optical properties. [6-29]

Docking can be defined as predicting both ligand conformation and orientation within a targeted binding site. Experimentally derived crystal and NMR protein structures are used as the basis for docking, and the physics involved is based on what is known about atomic and molecular interactions, as well as laws of thermodynamics.

All docking methods must include sampling ligand conformations, generating poses of the ligand within the receptor binding site, and scoring the poses. Because the process of finding a novel compound showing bioactivity can become time-consuming and expensive, structure-based drug design has been established as a vital first step to therapeutic development. Screening for ligand conformations can be performed using a ligand-based or a structure-based approach. [15-29]

Many of the methods reported for the synthesis of organic compounds are associated with the use of hazardous organic solvents, long reaction time, use of toxic catalysts, and lack of general applicability. Thus, development of a mild, neutral, and reusable catalyst for one-pot synthesis of novel pyranothiazole derivatives is an attractive goal for researchers.[30-40] In this paper, we report Cu NP in ionic liquid - catalyzed synthesis of pyranothiazole derivatives via a one-pot three component condensation of aldehydes, cyanoethylacetate and thiazlidine-2,4-diones (Scheme 1). Presence of these moieties in organic molecules imparts them with the extensive range of biological and pharmacological properties. Further, docking study of thiazolopyrans on

human pancreatic lipase related protein 1 receptor co-crystallized using iGEMDock was carried out.



Scheme 1 Synthesis of thiazolopyran (4a) using Cu NPs in IL

Experimental

Reagents and analysis

All reactions were carried out at ambient temperature in oven-dried glassware. The materials were purchased from Sigma-Aldrich and Merck used. The metal nanoparticles were systematically characterized by powder X-ray diffraction, transmission electron microscopy (TEM) and quasi elastic light scattering (QELS) techniques. Nanosize and morphology of the palladium and lead nanoparticles were observed under Philips TECNAI – FE12 Transmission Electron Microscope (120 kV). The particles were dispersed in methanol and a drop of it was placed on Formvar-coated copper grid followed by air-drying. The X- ray diffraction patterns were recorded using a RIGAKU ROTAFLEX RAD-B by Rigaku corporation Japan diffractometer using Cu target CuK (α) 1 radiation with tube voltage 40KV and 60mA in 2θ ranging from 5° to 60°.

Synthesis of Cu nanoparticles

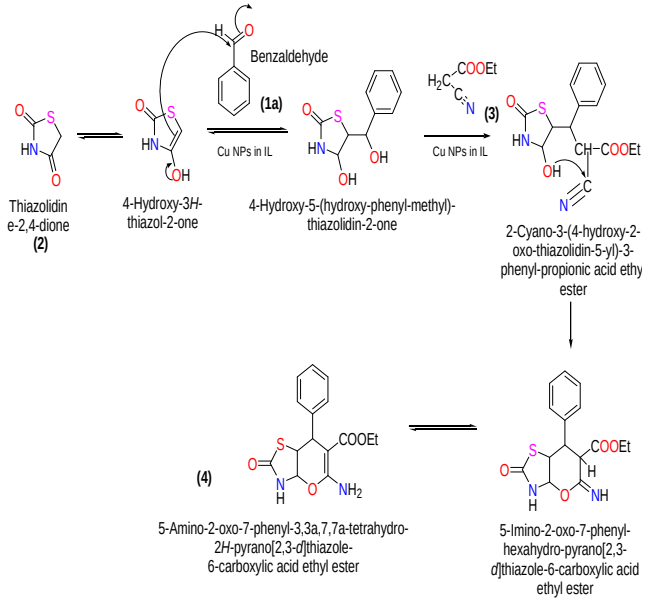
Cu NPs were synthesized by reducing copper nitrate in ionic liquid with methanolic solution of sodium borohydride. Briefly, copper nitrate (20mg) and tetrazolium ring based ionic liquid (5 mL) were stirred at room temperature. Then, excess of methanolic solution of sodium borohydride was added to the above solution. Suddenly a black colour solution was observed indicates the formation of Cu (0) particles. [6-14]

Optimization of the solvent for the synthesis of 5-Amino-2-oxo-7-phenyl-3, 3 a, 7, 7a-tetrahydro-2H-pyrano [2, 3-d] thiazole-6-carboxylic acid ethyl ester using Cu NPs

At the first, the synthesized Cu NPs have been tested for the synthesis of 5-Amino-2-oxo-7-phenyl-3,3a,7,7a-tetrahydro-2H-pyrano[2,3-d]thiazole-6-carboxylic acid ethyl ester (4a) via one pot three component reaction of thiazolidine-2,4-dione, cyanoethylacetate and benzaldehyde in different solvents at room temperature.

A mixture of aldehyde (1 mmol), cyanoethylacetate (1mmol) and thiazolidine-2, 4- Dione and Cu NPs (10 mg) in solvent was stirred at room temperature until completion of reaction (TLC-control). Next, the reaction mixture was centrifuges and the filtrate was taken and water was added to it.

Then the product was extracted with ethyl acetate (3x30 mL). Further it was washed with brine solution (3x30 mL). The solvent was evaporated under reduced pressure to afford a solid product, which was recrystallized from hot ethanol to obtain a pure product, 4a and the proposed mechanism for the synthesis of 4a is described in Scheme 2.



Scheme 2 Proposed mechanism for the synthesis of product 4a

It was found that Cu NPs in ionic liquid gave the maximum yield in minimum duration of time as in Table 1. Interestingly, formation of complex was found when we used no solvent. Similarly, a series of pyranothiazole derivatives (4) were synthesized from a variety of aromatic aldehydes (Table 2, entries 2–12) with cyanoethyl acetate and thiazolidine-2,4-dione easily only 10 mg of Cu NPs in ionic liquid (for 1mmol of aldehyde). The results presented in Table 2 indicate very short reaction times (15–30 min) and high yields (86–98%). The reaction products were characterized by their melting points and ^{1}H and ^{13}C NMR.

Table 1 Optimization of catalytic system for the multicomponent synthesis of thiazolopyrans (4a) at room temperature using copper nanoparticles in ionic liquid

S. No	Solvent	t (min)	Temp. (^{0}C)	Yield (%)
1	Dioxane	18	30	75
2	CH_3CN	15	30	78
3	DMF	24	30	52
4	Toluene	16	30	70
5	Et_3N	20	30	45
6	None	24	30	Complex
7	DMSO	24	30	50
8	THF	14	30	60
9	Tetrazolium ring based IL	10	30	90
10	CH_3CN	15	50	80
11	Cu NPs in IL	10	30	95

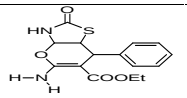
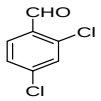
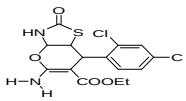
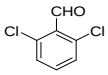
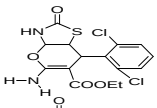
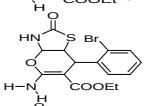
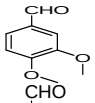
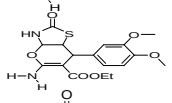
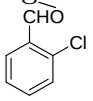
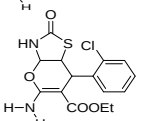
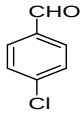
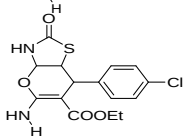
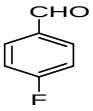
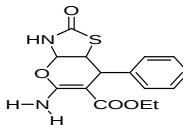
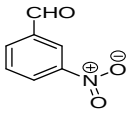
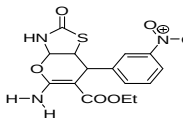
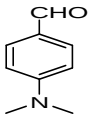
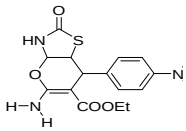
Computational study of thiazopyrans as human pancreatic lipase related protein 1 agonist

Optimization of thiazolopyrans

All the thiazolopyrans **(**18 compounds) were drawn on Chem Draw and were imported to Chem Draw 3D followed by their optimization using MOPAC (a computational tool) suing

AM1 calculation and closed shell restricted with RMS gradient 0.1.

Table 2 Synthesis of pyranothiazoles (4) via one pot three component reactions of thiazolidine-2, 4-dione, cyanoethylacetate and aldehydes using Cu NPs in IL

S. No.	Reactant (1)	Product (4)	Compound	Time (min)	Yield (%)
1			4a	10	95
2			4b	12	92
3			4c	14	93
4			4d	15	92
5			4e	9	95
6			4f	18	94
7			4g	20	92
8			4h	18	90
9			4i	9	94
10			4j	16	90

Protein Preparation

The crystal structure of human pancreatic lipase related protein 1 receptor having PDB ID: 2PPL was taken (http://www.rcsb.org/). The protein was prepared using Molegro Molecular Viewer 2.5 and the same was used for the virtual drug screening.

Docking studies

Herein, iGEMDock was used for the ligand docking as explained in Table 3. IGEMDock is a molecular docking tool and generates diversity of thiazolopyrans conformations from different seeds with high temperature molecular dynamics. Then, it orients the thiazolopyrans conformations within the defined protein active site by translating the center of the surfactant. Each orientation is subjected to simulated annealing molecular dynamics and sorted according to the interaction energy. IGEMDOCK energy function consists of electrostatic, steric, and hydrogen- bonding potentials. Steric and hydrogen bonding potentials use a linear model. There are four main steps which are used here.

Parameters used for drug screening in iGEMDOCK were as followed: initial step sizes (σ= 0.8 and ψ= 0.2), family competition length (L=2), population size (N=200), and recombination probability (pc=0.3). Optimization is set to generate 70 iterations for which it generated 1200 solutions in one generation process and if exceeded then it terminated after 84,000 solutions.

RESULTS AND DISCUSSION

Herein, Cu NPs in IL was used as efficient catalytic system for the synthesis of biological potent symmetrical and asymmetrical thiazolopyrans. A mixture of aromatic aldehyde, cyanoethyl acetate and thiazolidinediones were reacted as in Entry 1, Table 2. The activity of catalytic system was compared with other as mentioned in Table 1 in terms of yield and duration of reaction. We observed that the Cu NPs in IL showed the best catalytic activity amongst all. Similarly, different thiazolopyrans have been prepared as in Table 2. The advantage of this method is that compounds as in Table 2 were obtained in quantitative yields directly without formation of any byproduct. The higher reactivity of the catalyst can be attributed to the larger surface area of Cu NPs. The catalyst was recovered from the reaction mixture by centrifugation, washed successively with ethanol, and dispersed in ionic liquid for subsequent reactions. The catalyst reusability has been checked for the synthesis of 5-Amino-2-oxo-7-phenyl-3, 3', 7, 7'-tetrahydro-2H-pyrano [2, 3] thiazole -6-carboxylic acid ethyl ester (Table 2, entry 1). Figure 1 showed that the catalyst could be reused up to eight times with a minimal loss in the yield (90%) of the product (4a).

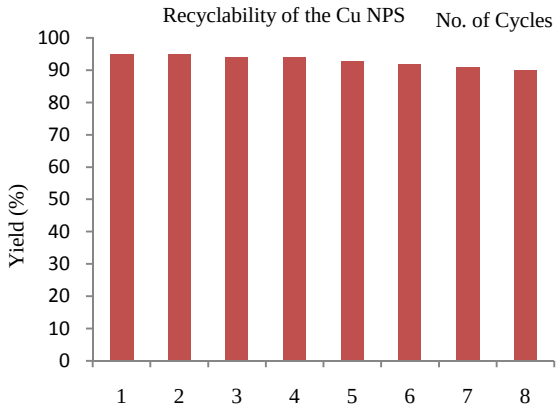


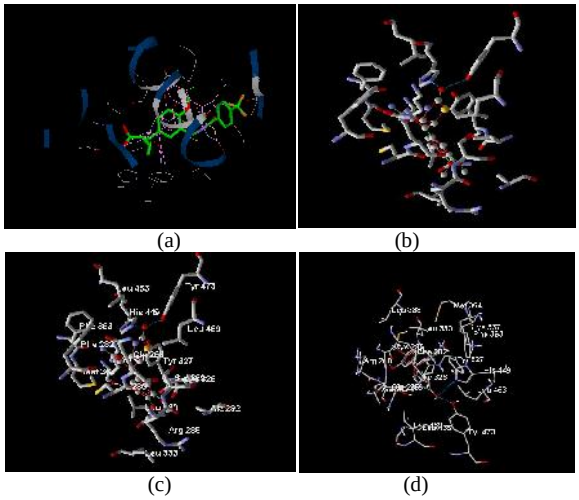
Figure 1 Recyclability of the Cu NPs for the synthesis of thiazolopyrans (4a)

Further, docking studies of thiazolopyrans have been carried out using computational tools, iGEMDock. Docking studies are used extensively in drug discovery such as in the prediction of ligand-ligand complex structures and also to rank the ligand molecules based upon the binding energies of the corresponding ligand-enzyme complex. The objective of our docking study is to elucidate the potential interaction mode of the thiazolopyrans with human pancreatic lipase

related protein 1. The binding energies of the best-docked inhibitor-enzyme complexes are shown in Table 3. A general conclusion derived from these docking results is that the side chain of the His 449 and Tyr 473 forms a hydrogen bond with the inhibitors as shown in Figure 2. The nature of these hydrogen bonds involves an interaction between the amidic nitrogen of human pancreatic lipase related protein 1and the nitrogen of thiazolopyrans. Interestingly, this interaction is almost conserved with all studied inhibitors. The docking calculations provided us with a general static picture of the most energetically favourable binding orientation of inhibitors to the enzyme. To obtain further insight into the dynamic changes of the docked inhibitors within the enzyme active site pocket over time, the lowest energy docked complex of the most active inhibitor, 5, was subjected to unconstrained MD simulations. The post dynamic monitoring of the overall hydrogen bond networks and the electrostatic interaction between the 5 inhibitor and nearby residue clearly revealed that these inhibitors settle comfortably inside the human pancreatic lipase related protein 1 active site

Table 3 Computational studies of thiazolopyrans as potent human pancreatic lipase related protein 1 inhibitor

C. No.	Energy	VDW	H Bond	E (pharma)	H-S-HIS-449	H-M-TYR-473	V-M-CYS-285	V-M-GLN-286
4a	-85.1	-72.976	-19.923	-105.8	-3.486	-2.5	-9.655	-5.223
4b	-85.1	-84.554	-15.392	-94.9	0	0	-7.875	-4.295
4c	-80.6	-84.146	-14.170	-83.3	0	0	-5.207	-0.1947
4d	-91.4	-84.924	-7.3847	-115.2	-4.306	-3.5	-6.340	-6.9016
4e	-103	-77.900	-7.2127	-123.2	-3.5	-2.5	-9.025	-5.129
4f	-102.3	-79.085	-6	-133.7	-4.607	-6.944	-6.454	-6.708
4g	-92.3	-83.059	-19.203	-113.4	-3.5	-2.5	-10.241	-5.574
4h	-99.9	-73.516	-7.0754	-121	-2.594	-3.5	-6.020	-5.719
4i	-92.5	-91.979	-10.981	-94.3	0	0	-3.615	-0.053
4j	-98.3	-75.265	-16.143	-116.4	-0.6476	-3.5	-6.3525	-5.845



(a) (b) (c) (d)

Figure 2 (a-d) showed the binding of thiazolopyrans (4e) with the human pancreatic lipase related protein 1 receptor

CONCLUSION

A series of biologically and pharmacologically active pyranothiazole derivatives have been synthesized using Cu NPs in ionic liquid as catalyst via one-pot three component condensation of an aldehyde, cyanoethylacetate, and thiazolidine-2,4-dione in excellent yields (90–95%) within a practical reaction time (9-20 minutes). The advantages offered by Cu NPs as catalyst versus known catalysts are (i) the catalyst is very mild and neutral, (ii) inexpensive, (iii) reusable, and (iv) environmentally benign. The exploration of Cu NPs as catalyst for other multicomponent reactions leading to biologically active compounds is underway. Further, computational studies of the synthesized compounds have been performed against human pancreatic lipase related protein 1 receptors and proposed them as potent agents. Among the all thiazolopyrans, compound no. 5 has shown potent atypical response against human pancreatic lipase related protein 1.

Analytical data of compound 4a

5-Amino-2-oxo-7-phenyl-3, 3a, 7, 7a - tetrahydro-2H-pyrano [2, 3-d] thiazole-6-carboxylic acid ethyl ester (**4a**), 80 %, Melting Point = 198^0C ^{1}H NMR (d-DMSO) = 1.26 (q, 3H, Methyl of ester), 2.10 (p, 2H, CH_2 of ester), 4.32 (d, 1H, benzylic C-H), 7.35 (q, t, 2H, *meta*-protons on phenyl ring), 7.89 (d, 2H, *ortho* proton on phenyl ring), 7.56 (q, 1H, *para* proton on phenyl ring), 2.64 (s, 2H, NH_2) , 12.15 (s, NH), 6.15 (s, CH), 4.36 (d, CH), ^{13}C NMR (d-DMSO) = 127.5 (Carbon of o-phenyl), 128.1 (Carbon of o-phenyl), 124.2 (Carbon of o-phenyl), 55.2 (benzyl carbon), 164.2 (carbonyl carbon of amide), 172.3 (carbonyl carbon of ester), 61.2 (CH2 of ester), 18.5 (CH_3 of ester), 168.7 (Alkenic carbon bonded to oxygen), 80.5 (alkenic carbon bonded to benzylic carbon), 140.1 (phenyl carbon bonded to benzylic carbon), Low Resolution Fast Atom Bombardment MS: Calculated for $C_{15}H_{16}N_2SO_4\,M^+ = 320.2164$

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