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Review on Computer-Aided Drug Design (CADD) Technique in Drug Discovery Researches and Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Ones/Thiones Catalyzed by Camphor Sulfonic Acid

Mohammad Amin Moragheb [1], Farzaneh Mohamadpour [2,*]

[1] Department of Computer Engineering, Mamasani Higher Education Center, Mamasani, Iran
[2] School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran
[*] Correspondence: mohamadpour.f.7@gmail.com (F.M.);

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Abstract: Combined with various computational and theoretical approaches, computer-aided drug design (CADD) is one of the contemporary approaches to drug discovery. Furthermore, this study briefly assesses the literature on computer-assisted drug design (CADD) techniques used in drug discovery research. An environmentally friendly synthetic route was developed for the convenient Biginelli synthesis of 3,4-dihydropyridine-2-(1*H*)-ones/thiones when no solvents are involved in the reaction using aromatic derivatives, urea/thiourea, and ethyl/methyl acetoacetate as catalysts in combination with camphor sulfonic acid (CSA). All reactions proceeded rapidly, and good product yields were obtained. Green synthesis in this study has many advantages over conventional synthesis, including a clean and environmentally friendly synthesis, easy operation, the elimination of hazardous organic solvents, a purification step free of chromatography, and the use of a non-corrosive and non-volatile catalyst. Furthermore, the method can be applied to single-tank reactions in a solvent-free environment.

Keywords: computer-aided drug design (CADD); camphor sulfonic acid (CSA); 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives; solvent-free conditions.

1. Introduction

Computer-aided drug design (CADD) is a growing trend, also referred to as in silico screening. CADD is an umbrella term that refers to the many computational and theoretical approaches utilized in contemporary drug development. This can be attributed to the fact that CADD is complex, making it valuable at various drug discovery and development stages. Computational scientists, structural biologists, and biophysicists identify novel chemical entities at the Center for Computer-Aided Drug Design (CADD). The present paper also includes a mini-review of the application of CADD techniques in drug discovery research [1,2].

The synthesis of heterocyclic compounds has attracted great interest due to their wide applicability in life and nature. The compounds with pyrimidinone derivatives are reported as anticancer drugs (Mal3-101) [3] and anti-HIV agents [4], as well as antibacterial and antifungal [5], antiviral [6], and antioxidative [7] agents. Researchers have found anticancer, antifungal [5], and anti-HIV activities in compounds such as batzelladines, ptilomycalines, and crambescidines [8].

During contemporary organic synthesis, green chemistry has been considered a significant factor, emphasizing increasing efficiency, reducing waste, minimizing byproducts, simplifying organic synthesis processes, and avoiding toxic chemicals in catalytic procedures. In addition, organic chemists have focused on the green and environmentally friendly synthesis of organic molecules through chemical reactions performed without using solvents. The recent focus has been developing green catalysts for multi-component processes [9-13].

Different methods have been reported in recent decades for preparation of these compounds including the use of various catalysts, e.g. calcium fluoride [14], copper(II)sulfamate [15], bakers' yeast [16], used to accelerate the synthesis of organic compounds, hydrotalcite [17], hexaaquaaluminium (III) tetrafluoroborate [18], TBAB [19], copper (II) tetrafluoroborate [20], Iron (III) tosylate [21], [Btto][*p*-TSA] [22], salicylic acid [23], triethylammonium acetate [24], potassium alum [25], *p*-dodecylbenzenesulfonic acid [26], TMSPTPOSA [27], fumaric acid [28] and TiO_2 NPs [29]. While several disadvantages of similar techniques were found, including the use of expensive and dangerous catalysts, complex procedures, very acidic environments, significantly lower yields than expected, and longer reaction times. A portion of our continuous inquiry about the program on the improvement of green strategies [30-44], herein, we report a green and one-pot methodology for synthesizing 3,4-dihydropyridine-2-(1*H*)-one/thione derivatives. Biginelli reaction [45] involves ketone, aromatic derivatives. This method reduces the reaction time significantly compared to previous methods, maintaining high to super yields while employing an environmentally friendly procedure, making it a viable option.

2. Materials and Methods

2.1. Experimental.

The melting points of all compounds were determined using an electrothermal 9100 device.DMSO-d_6 was used as a solvent for the ^{1}HNMR spectra obtained on a Bruker DRX-300 Avance spectrometer. Merck, Fluka, and Acros provided the reagents and solvents used in this study.

2.2. General procedure.

An aromatic aldehyde derivative mixture (1, 1.0 mmol), urea/thiourea (2, 1.5 mmol), and ethyl/methyl acetoacetate (3, 1.0 mmol) were heated to 70°C under the presence of camphor sulfonic acid (15 mol%) without solvent for five minutes. As soon as the thin layer chromatography (TLC) reaction was complete, in this experiment, cold water was added to the mixture to bring it to room temperature (rt). The precipitate was removed from the ethanol by filtration and recrystallization to yield the pure product (4a-s). This section contains spectra of many well-known commercial products.

5-Ethoxycarbonyl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)–one (4c):

Yield: 94%; M.p. 172-174 °C; ^{1}HNMR (300 MHz, DMSO-d_6): 1.07 (3H , t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.34 (3H, s, CH_3), 4.06 (2H, q, *J*=7.2 Hz, CH_2O), 5.27 (1H, s, CHN), 6.87 (2H, d, *J*=7.2 Hz, ArH), 7.41-7.53 (2H, m, ArH), 7.92 and 9.36 (2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)–one (4m):

Yield: 87%; M.p. 243-245 °C; ^{1}HNMR (300 MHz, DMSO-d_6): 2.26 (3H, s, CH_3), 3.58 (3H, s, OCH_3), 5.16 (1H, s, CHN), 6.73-7.08 (2H, m, ArH), 7.13-7.25 (2H, m, ArH), 7.81 and 9.05 (2H, 2s, 2NH), 9.24 (1H, s, OH).

3. Results and Discussion

3.1.Computer-aided drug design (CADD) technique in drug discovery studies.

While drug discovery and development is a time-consuming, costly, and complex process, introducing computer tools and techniques has expedited the process. Designing drugs with computer assistance (CADD) or screening them in silico has emerged as an effective method in recent years. This is primarily due to the sophisticated characteristics of CADD, which have made it helpful in different stages of drug discovery and development [1].

CADD encompasses a wide variety of computational and theoretical methods used in contemporary drug discovery and has made significant contributions to drug development at clinical use and clinical trial phases. They have evolved in lockstep with experimental methods for drug discovery [2].

Drug development is a highly complex process that utilizes an interdisciplinary approach to develop effective and economically viable medicines. Computers are critical in scientific research in general, particularly in the pharmaceutical and medical sectors, particularly in creating novel chemicals to develop more effective treatments. When coupled with structural biology, rational drug design can develop novel therapeutic medicines [1]. To do this, the CADD Centre fosters cooperation between academics from many fields, including structural biologists, biophysicists, and computer scientists, to find novel chemical compounds. In conjunction with bioinformatics technologies, CADD may provide benefits such as cost-effectiveness, decreased time to market (TTM), increased understanding of drug-receptor interactions, and acceleration of drug discovery and development. It takes years to find and develop a new medication. The process involves scientific research to identify the illness, the particular target receptor, and the active molecules among many chemicals [1].

CADD techniques are used to analyze the target structure (to identify potential binding sites), generate candidate molecules, conduct molecular docking with the target, rank candidate molecules according to their bio-affinities, and optimize the molecules for future enhancement. CADD has been used in many phases of drug discovery, including research and development, target identification and validation, and preclinical studies (Pharmacokinetic; ADMET prediction). The use of cutting-edge technology, such as automation and high-throughput screening (HTS), enables the rapid identification of new drugs by synthesizing millions of molecules in a short amount of time. It takes about 7-12 years and $ 1.2 billion to develop a new medication approved for commercial use. Additionally, about five out of every 40,000 novel medicines reach the preclinical testing stage, and one out of every five reach the clinical trial stage [1].

3.2.Using CADD to seek for and develop multi-targeted drugs.

CADD is advantageous for searching for medicines against many targets since multiple hits are produced against multiple targets. True-hit rates against targets must be greater than false-hit rates since this is needed for multi-target enrichment searching [1].

The CADD method for developing pharmacophores: Pharmacophore is best described as an organic compound's bioactivity determined by the spatial arrangement of its functional groups. The pharmacophore development model is an integral part of the drug research, design, optimization, and development processes. CADD may screen for pharmacophores since it includes molecules with varying scaffolds but comparable three-dimensional functional group

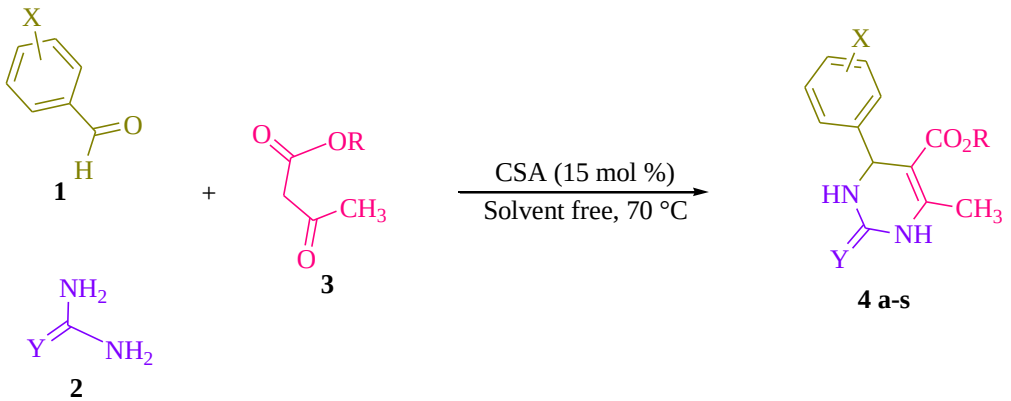
organization. Pharmacophore techniques are used to identify several kinds of chemicals that have a similar structure. Before using the produced pharmacophore, it should be verified against external data. Virtual screening is carried out until a suitable pharmacophore is formed [1].

3.3.CADD is used to generate conformations.

The conformational production of small molecules is critical in the design and development of drugs because it determines their physical and biological characteristics. The conformer must possess the necessary energy and binding affinity for a particular target. Cyndi is a fast technique for generating conformations that are based on MOEA or multi-objective evolutionary algorithms. Cyndi continuously scans the conformational space and regulates geometric variety and energy accessibility through MOEA. Another technique for generating conformations is Macro Model, which is incorporated into MaestroV7.5 (Schrodinger Inc.). It differs from Cyndi within conformational cost and depth of sampling in conformational space [1].

3.4. Biginelli synthesis of 3,4-dihydropyridine-2-(1H)-ones/thiones.

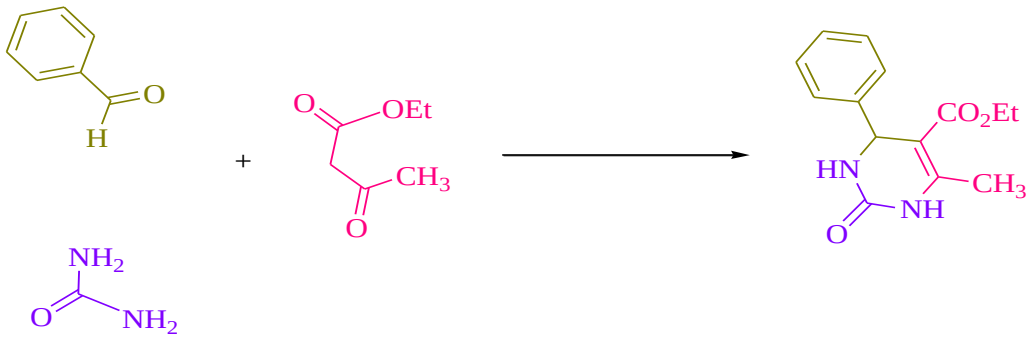
First, a three-component condensation of benzaldehyde (1.0 mmol), urea (1.5 mmol), and ethyl acetoacetate (1.0 mmol) were carried out at 70 °C in the presence of camphor sulfonic acid (15 mol%) in an environment that is free of solvents. Product 4a was found at that time at 91%. The above reaction was used as a model to understand better the conditions required to synthesize 3,4-dihydropyridine-2-(1*H*)-one/thione derivatives (4a-s). The amount of catalyst required to maximize the reaction conditions was calculated. Despite removing the catalyst for 180 minutes, no product could be determined (Table 1, entry 1). In this reaction, the catalyst significantly increased yield and rate. The reactions were then carried out with the addition of 5 mol% CSA, leading to longer reaction times and lower yields (Table 1, entry 2). As a result, the catalyst loading gradually increased from 5% to 20% (Table 1). According to the study results, 15 mol% CSA is the optimal amount to complete the reaction in a short period (Table 1, entry 4). A higher catalyst concentration did not influence the reaction time and yield. Therefore, 15% mol% CSA is the most effective way to obtain the desired product with high yields. Additionally, model reactions at different temperatures were investigated (Table 1). Increasing the temperature from RT to 80°C caused a rapid reaction, significantly increasing the desired product yield (Table 1).



Scheme 1. A synthetic method of 3,4-dihydropyrimidin-2-(1*H*)-ones and thiones.

This study found that the reaction proceeded efficiently and that the reactants were wholly converted to the desired product (4a) in 15 minutes at 70°C in 91% yield (Table 1, entry 4). The product yield did not change with an increase in temperature (Table 1, entry 9). When the conditions of the reactions have been optimized, a series of 3,4-dihydropyridine-2(1*H*)-one/thione derivatives (4a-s) were produced under solvent-free conditions using aromatic aldehyde derivatives (1, 1.0 mmol), urea/thiourea (2, 1.5 mmol), and ethyl/methyl acetoacetate (3, 1.0 mmol) at 70°C.

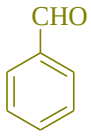
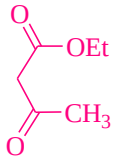
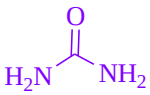
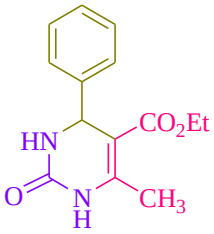
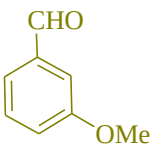
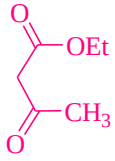
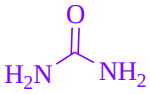
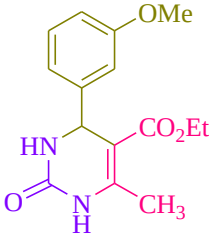
Table 1. Synthesis of 4a by optimizing the reaction conditions[a]

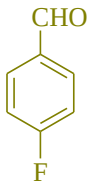
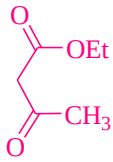
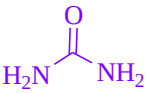
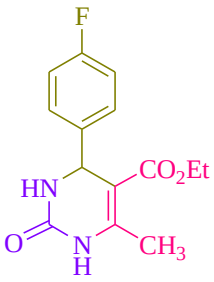
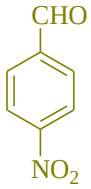
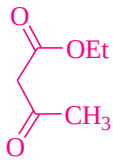
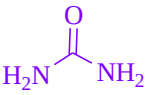
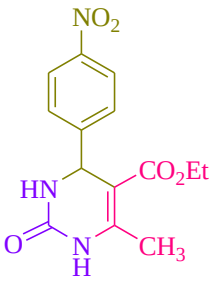
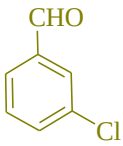
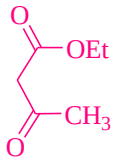
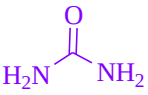
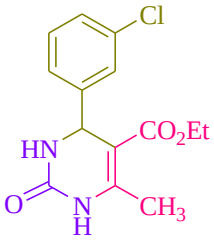
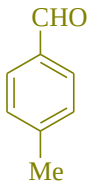
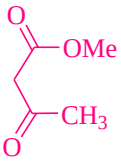
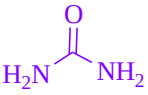
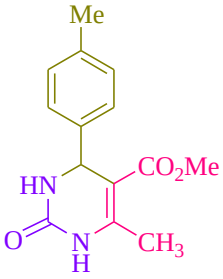
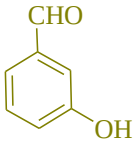
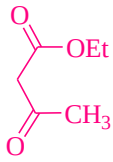
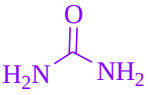
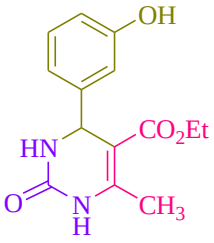
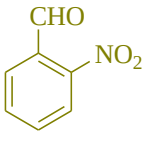
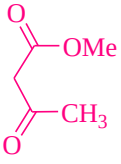
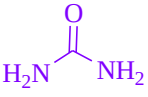
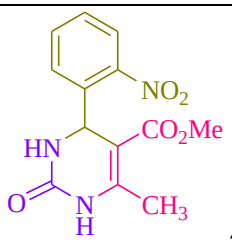


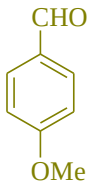
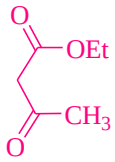
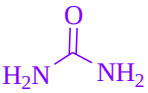
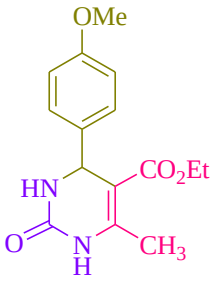
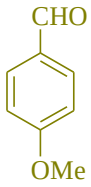
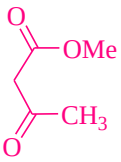
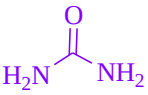
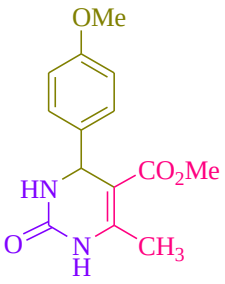
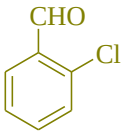
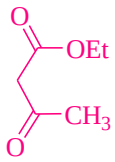
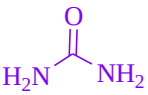
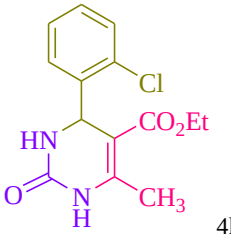
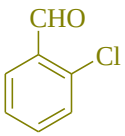
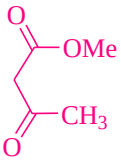
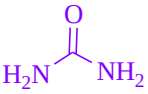
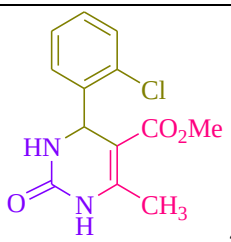
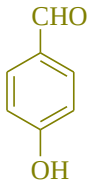
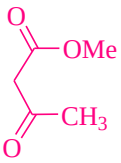
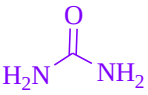
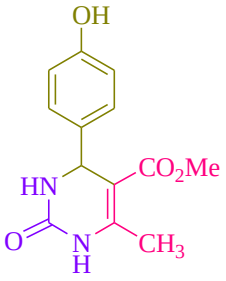
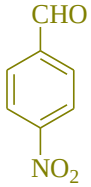
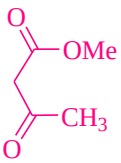
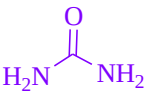
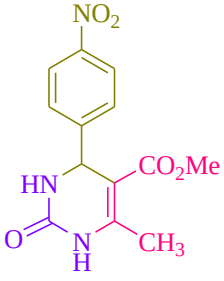
Entry	CSA (mol %)	Temperature (°C)	Time (min)	Isolated Yields (%)
1	Catalyst free	70	180	No product
2	5	70	35	52
3	10	70	20	76
4	15	70	15	91
5	15	rt	180	No product
6	15	40	45	35
7	15	50	30	56
8	15	60	20	73
9	15	80	15	91
10	20	70	15	92

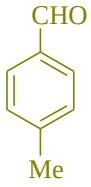
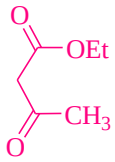
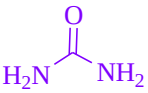
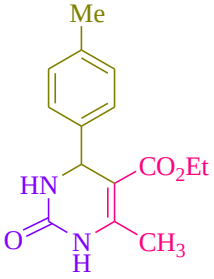
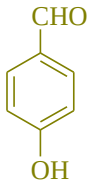
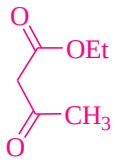
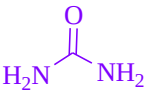
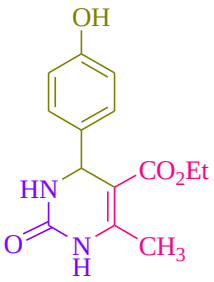
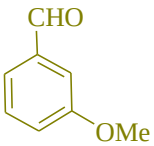
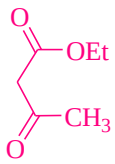
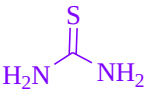
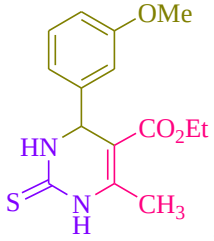
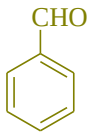
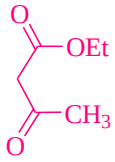
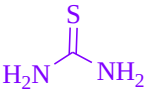
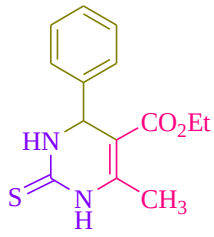
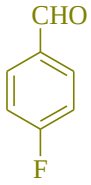
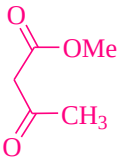
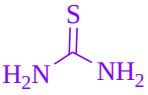
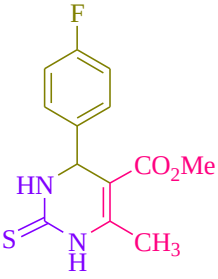
[a] Reaction conditions: A combination of benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol), and one CSA was heated to the appropriate temperature for the reaction to take place.

Table 2. CSA-catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.°C	Lit. m.p.°C
1				 4a	15	91	199-201	200-202 [15]
2				 4b	20	88	206-208	205-206 [16]

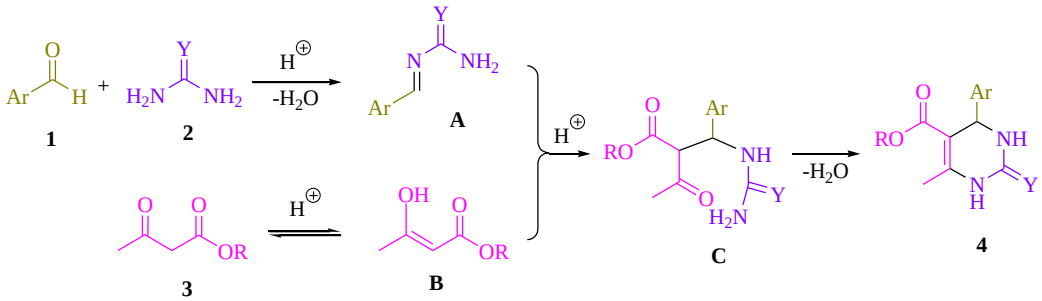
Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.°C	Lit. m.p.°C
3				 4c	10	94	172-174	174-176 [19]
4				 4d	15	92	205-207	207-209 [15]
5				 4e	20	86	192-194	191-193 [25]
6				 4f	10	94	202-204	200-203 [20]
7				 4g	25	83	161-163	163-166 [20]
8				 4h	10	90	275-277	274-277 [20]

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.°C	Lit. m.p.°C
9				 4i	25	85	204-206	203-205 [22]
10				 4j	20	87	191-193	190-194 [20]
11				 4k	20	82	222-224	220-223 [15]
12				 4l	20	85	249-251	248-252 [15]
13				 4m	25	87	243-245	245-246 [16]
14				 4n	15	94	215-217	214-216 [15]

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.°C	Lit. m.p.°C
15				 4o	15	93	202-204	204-205 [16]
16				 4p	25	85	231-233	229-231 [28]
17				 4q	20	85	150-152	150-151 [16]
18				 4r	20	89	207-209	208-210 [15]
19				 4s	15	91	210-212	208-210 [19]

[a] Reaction conditions: arylaldehyde derivatives (1.0 mmol), ethyl/methyl acetoacetate (1.0 mmol), urea/thiourea (1.5 mmol) and CSA (15 mol %) were heated at 70 °C. [b] Isolated yield.

As shown in Scheme 2, a proposed route can be used in the presence of CSA to synthesize 3,4-dihydropyridin-2(1*H*)-ones/thiones.



Scheme 2. The proposed mechanistic route for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones.

Table 3. Comparative analysis of the catalytic properties of many catalysts described in the literature for the production of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones[a]

Entry	Catalyst	Conditions	Time/Yield (%)/[References]
1	Bakers' yeast	Room temperature	24 h/84 [16]
2	hydrotalcite	Solvent-free, 80 °C	35 min/84 [17]
3	$[Al(H_2O)_6](BF_4)_3$	MeCN, Reflux	20 h/81 [18]
4	$Cu(BF_4)_2.xH_2O$	Room temperature	30 min/90 [20]
5	[Btto][*p*-TSA]	Solvent-free, 90°C	30 min/96 [22]
6	triethylammonium acetate	Solvent-free, 70 °C	45 min/90 [24]
7	*p*-dodecylbenzenesulfonic acid	Solvent-free, 80 °C	3 h/94 [26]
8	TMSPTPOSA	EtOH/Reflux	3 h/95 [27]
9	camphor sulfonic acid	Solvent-free, 70 °C	15 min/91 [This work]

[a] In three components, benzaldehyde, ethyl acetoacetate, and urea are heated to form a reaction.

4. Conclusions

CADD is a broad term that encompasses many computational and theoretical approaches used in contemporary drug development. In addition, this paper includes a mini-review of the application of CADD techniques in drug discovery research. Also, This study provides an eco-friendly method in which 3,4-dihydropyridine-2-(1*H*)-one/thione derivatives can now be synthesized in one pot with three ingredients using camphor sulfonic acid (CSA) under solvent-free conditions. It has many advantages, including high to super-yield, fast reaction time, simple column-free setup, high catalytic activity, environmentally friendly, solvent-free conditions, and easily accessible components.

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Acknowledgments

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Conflicts of Interest

The authors declare no conflict of interest.

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