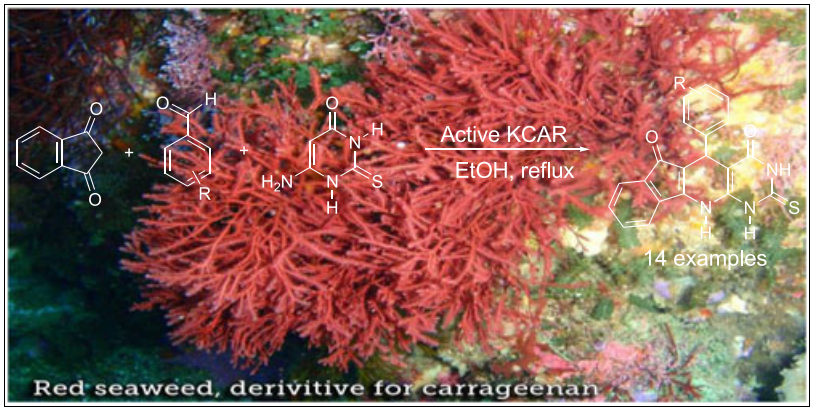
Modified Kappa-Carrageenan as a Heterogeneous Green Catalyst for the Synthesis of Nitrogen and Sulfur-Containing Indenone-Fused Heterocyclic Compounds

Mohammad Bayat* and Shima Nasri

Department of Chemistry, Imam Khomeini International University, Qazvin, Iran
*E-mail: bayat_mo@yahoo.com, m.bayat@sci.ikiu.ac.ir

Received September 12, 2017
DOI 10.1002/jhet.3083
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



The three component reaction of aromatic aldehydes and 1,3-indandione in the presence of 4-amino-6-hydroxy-2-mercaptopyrimidine is catalyzed by active kappa-carrageenan under mild conditions to afford the desired products in clean reaction profiles. The kappa carrageenan sources are bioavailable and are extracted from *Chondrus crispus*, a red seaweed. The catalyst could be prepared by mixing of kappa-carrageenan in a mechanical mortar for 5 min in a simple step. Good yields with superior atom economy, green and recyclable catalyst with natural source, and simple work-up are the main advantages of the method for the synthesis of dihydropyridopyrimidines.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

The "greening" of chemical processes has become a significant topic in the chemical industry because of rising environmental pollution, in terms of acceptable chemicals, catalysts, solvents, atom efficient procedures, and new energy sources [1–5]. In this regard, the use of new eco-friendly organocatalysts and replacement petrochemical-based raw materials by biological materials [6] in organic synthesis have appeared as issues of innovation in green chemistry for production of fine chemicals [7].

Carrageenans are natural and biodegradable polymer with water-soluble, linear, sulfonated galactans that the "original" carrageenan was *Chondrus crispus*, a red seaweed found in the north Atlantic, which is mainly used in the food industry as gelling agent, drug-delivery cases, and some applications in the toiletries industry. Industrial applications of carrageenan are rare [8,9]. The cation of this anionic polysaccharide is usually K^+ or Na^+ whose structure contains galactose, 3,6-anhydrogalactose units, carboxy and hydroxy groups and ester sulfates as active catalytic centers, possesses interesting properties, nontoxic and biodegradable, and it contains metal anchoring functional groups [10–12]. There are three types of carrageenan depending on the number of charged sulfated groups per biopolymer repeat unit, that is, kappa carrageenan (KCAR) (one group), iota-carrageenan (two groups), and lambda-carrageenan (three groups) [13]. KCAR is the most commonly used type of carrageenan (Fig. 1).

Kappa-carrageenan has been applied more as a catalyst in organic syntheses with post modification, due to its high affinity to metal ions [14,15] and as heterogeneous catalysis systems that provide the advantages of easy catalyst removal and recycling [16,17]. But nowadays, many methods have been used in order to eliminate the use of transition metals in chemical reactions due to their toxicity and the difficulty in separating of metal catalysts [18,19].

In 1943, Astwood realized the high antithyroid activity and low toxicity of 2-thiouracil, and many derivatives of this compound have been synthesized and tested their physiological activity [20–22]. Amino-uracil derivatives especially 6-Amino-2-thiouracil display very important classes of functionalized uracils. In addition, 6-amino-uracil derivatives find wide usages as starting materials for the synthesis of a number of fused uracils of biological importance, for example, pyrano-pyrimidine, pyrido-

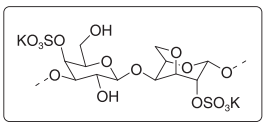


Figure 1. Chemical structure of kappa carrageenan.

pyrimidine, pyrazolo-pyrimidine, pyrimido-pyrimidine, and pyridazino-pyrimidine [23,24]. In the synthesis of drugs, 6-amino-thiouracil compound is superior to 6-amino-1,3-dimethyluracil because there are numerous hydrogen bonding possibilities, unlike in the structure of 1,3-dimethyluracil. These compounds are structurally similar to normal metabolites, and they can easily be mistaken for metabolic activities by biological systems [25].

The pyrido[2,3-*d*]pyrimidines present a considerable interest for research because being an important class of *N*-heterocycles that exhibits a wide range of potential biological activities and have established utility in the pharmaceutical and the agrochemical industries [26,27]. These compounds possess various pharmacological activity such as antitumor [28,29], cardiotonic [30,31], hepato-protective [30], antihypertensive [30], antibronchitic [32], antifungal [33], antibacterial [34], and antifolate [35] and calcium channel antagonist activities [36], anti-inflammatory [37], antipyretic [38], analgesic [39] and in treatment of diarrhea [40] and antileukemic activity [41] (Fig. 2).

Therefore, these fused heterocycles have been widely surveyed, and their synthetic methods are well-recorded [42–44]. They usually require drastic conditions [45], like long reaction times [46,47], and multistep complex synthetic pathways [29]. For all these observations and in continuing the others previous work on the synthesis of fused pyrimidines for biological evaluations [48], new routes for the synthesis of a series of polyfunctionally fused pyrimidines are explained [49,50]. The reactions of 6-aminothiouracil with 1,3-diketone compounds are the most general methods because both forms pyrido[2,3-*d*] pyrimidines and their dihydro derivatives with different substituents in positions 5 and 7 of the heterocyclic system can be achieved [27].

Encouraged by these reports of the importance of *N*-substituted 6-amino-2-thiouracils with respect to their antitumor activity, we have developed a simple and high yielding eco-compatible diversity oriented multicomponent synthetic method for the preparation of new nitrogen and sulfur-containing dihydropyridopyrimidines (DHPs).

RESULTS AND DISCUSSION

The one-pot three-component reaction of aromatic aldehydes, 1,3-indandione, and aminothiouracil in the presence of a heterogeneous and green catalyst in ethanol under reflux condition leads to afford corresponding DHPs derivatives **5** in good yields (Scheme 1). To the best of our knowledge, there are two reports on the synthesis of these compounds by using 1,3-indandione as a CH-acid in the literatures. Previous synthetic methods for producing these compounds are reported as follows: in 2010, El-Shafei et al. have reported synthesis of 2-thioxo-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine in DMF as reaction solvent [51]. In 2007, Hassaneen reported synthesis of pyrimidine related derivatives in absolute ethanol in the presence of piperidine as a catalyst [52]. Almost all of these procedures suffer from certain drawbacks such as toxic solvents and toxic catalysts.

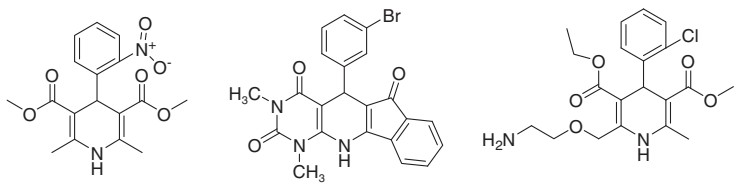
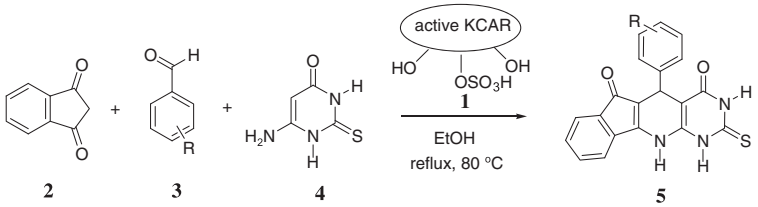


Figure 2. Some pharmacological examples with pyrido[2,3-*d*]pyrimidines framework.

Scheme 1. General synthesis of substituted dihydropyridopyrimidine.



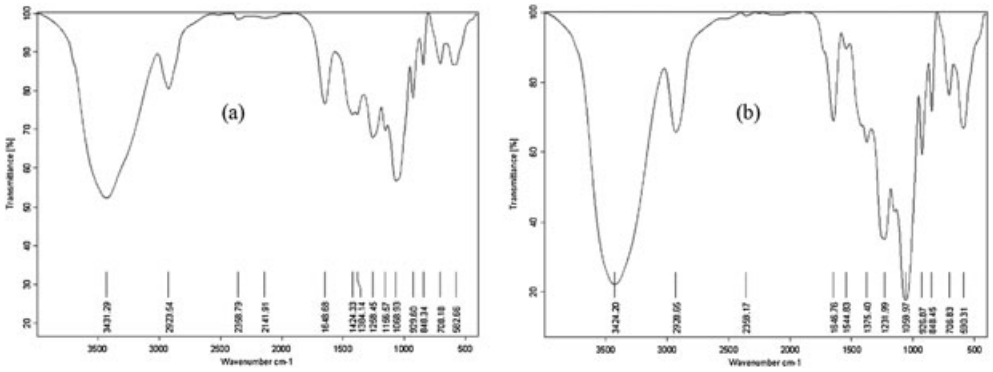


Figure 3. Infrared spectrum of (a) kappa carrageenan and (b) active kappa carrageenan.

So in this article, we used KCAR as the catalyst without post modification for the synthesis of new 1,4-DHPs. To best of our knowledge, this was the second study in which KCAR was merely applied as a catalyst with no need for post modification [11].

However, in order to produce Bronsted acid of KCAR (active KCAR), the K^+ ions of $-SO_3K$ moieties in KCAR should be exchanged with H^+, furthermore, hydroxyl groups of KCAR are able to create hydrogen bonding with the reactants and activate them. KCAR acted as a heterogeneous catalyst in ethanol because this biopolymer only was soluble in hot water.

Maintenance of every functional group within the activated KCAR could be easily monitored by infrared (IR) spectra results of KCAR and active KCAR by the appearance of a broadband around 3424 cm^{-1} corresponding to sulfonic acid and hydroxyl groups (Fig. 3).

In order to optimize the reaction conditions and find a catalyst effective for the synthesis of the 5-phenyl-2-thioxo-2,3,5,11-tetrahydro-1*H*-indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-4,6-dione derivatives, we examined this condensation reaction in the various parameters, such as absence and the presence of several catalysts, amount of catalyst, and several solvents. The optimized results are presented in Table 1. It was observed that the yields of isolated product were good when nano SiO_2 (20%), nano TiO_2 (20%), and KCAR (30%) were used as catalyst in ethanol (Table 1, entries 2, 3, and 9). But when the reaction was performed with the use of KCAR in ethanol, the desired product was obtained in shorter reaction time than that obtained with the use of other catalysts (Table 1, entries 8 and 9). The results clearly indicate that KCAR (30%) shows superiority over the other systems as to catalyzed the reaction efficiently to facilitate the synthesis of pyrido[2,3-*d*]pyrimidine in excellent yields and shorter reaction time (Table 1, entry 9). A different result was obtained when *p*-Toluenesulfonic acid or KCAR in aqueous condition was used. In the case of *p*-Toluenesulfonic acid as catalyst, 1,3-indandione is not involved in the reaction and main product resulting from the reaction between the aldehyde and 6-amino-2-thiouracil in 95% efficiency (Table 1, entry 5), but when using KCAR in aqueous condition, because of the lack of

Table 1

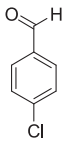
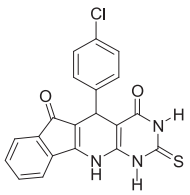
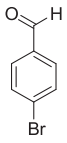
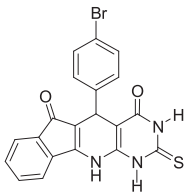
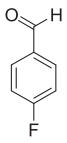
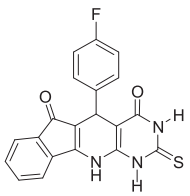
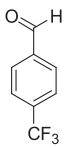
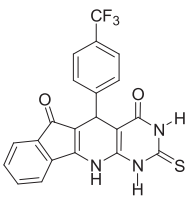
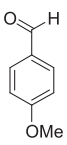
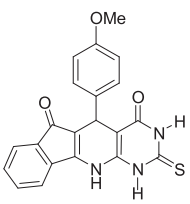
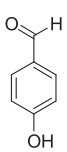
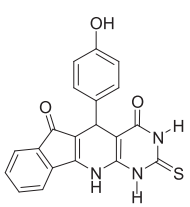
Catalyst effect on the reaction[a].

Entry	Catalyst (mol %)	Solvent	T(°C)	Time (h)[b]	Yield (%) [c]
1	None	EtOH	Reflux	8	67
2	Nano SiO_2 (20%)	EtOH	Reflux	2.5	95
3	Nano TiO_2 (20%)	EtOH	Reflux	2.5	90
4	Nano TiO_2 (30%)[d]	EtOH	Reflux	3.5	60
5	*p*-TSA (20%)[e]	EtOH	Reflux	-	No reaction
6	Kappa carrageenan (20%)[e]	H_2O	Reflux	-	No reaction
7	Kappa carrageenan (20%)	MeOH	Reflux	3	84
8	Kappa carrageenan (20%)	EtOH	Reflux	1	85
9	Kappa carrageenan (30%)	EtOH	Reflux	1	94

p-TSA, *p*-Toluenesulfonic acid.
[a]A mixture of 1,3-indandione (1 mmol), 4-chlorobenzaldehyde (1 mmol) and 6-amino-2-thiouracil (1 mmol) in different conditions.
[b]Reaction time is recorded based on the appearance of sediment (end time of the reaction).
[c]Isolated yields.
[d]Because of hydroxylation of the catalyst, there is inhibitory effect in high doses.
[e]Different product was obtained.

Table 2

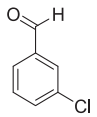
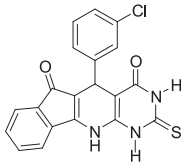
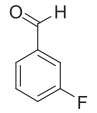
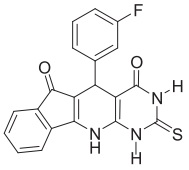
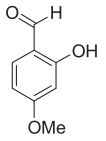
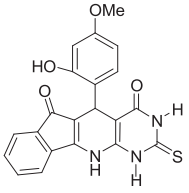
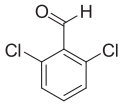
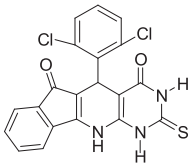
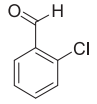
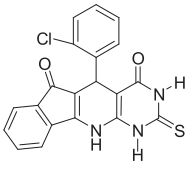
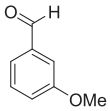
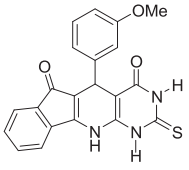
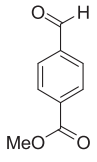
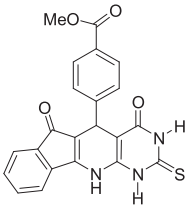
Synthesis of dihydropyrido[2,3-*d*]pyrimidines **5a–5k.**

Entry	Aldehyde	Product	Time (h) (No catalyst)	Time (h) (KCAR 30%)	Yield (%) (No catalyst)	Yield (%) (KCAR 30%)	Mp (°C)
5a			8	1	67	94	>330
5b			7	1	58	82	>330
5c			9	2	62	86	>330
5d			10	2.5	48	65	264–266
5e			11	2.5	52	72	330–332
5f			12	2	40	61	322–323

(*Continues*)

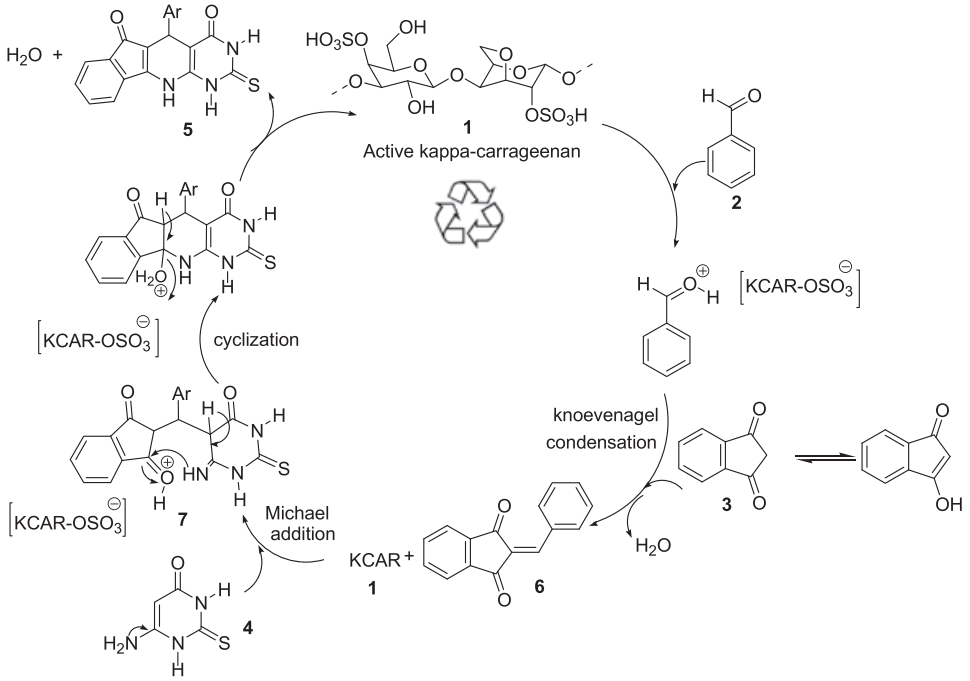
Table 2

(*Continued*)

Entry	Aldehyde	Product	Time (h) (No catalyst)	Time (h) (KCAR 30%)	Yield (%) (No catalyst)	Yield (%) (KCAR 30%)	Mp (°C)
5g			7	1	60	82	325–327
5h			10	2	72	88	>330
5i			12	2.5	81	93	>330
5j			9	2	69	82	>330
5k			7	1.5	72	88	320–322
5l			9	2	65	80	328–330
5m			8	1	82	95	> 330

KCAR, kappa carrageenan.

Scheme 2. Proposed mechanism for the formation of compounds **5**.



solubility of 6-amino-2-thiouracil in water, the reaction is not complete. It should be mentioned that when the reaction was carried out in the absence of catalyst under reflux in ethanol, it takes for long period of time even up to 12 h, and the yield of product was very low.

The reaction was completed after 1–2.5 h in refluxing ethanol promoted by active KCAR to afford corresponding heterocyclic systems **5a–5m**, in moderate to good yields (61–95%). The structures of the separated crude products **5a–5m** were clearly deduced from their IR, ^{1}H and ^{13}C NMR spectra. Because the product **5** is insoluble in ethanol, so easily be purified by filtration and washing with ethanol, column chromatography is unnecessary. As shown in Table 2, several functionalities present in the aryl moiety such as halogen, hydroxyl, and methoxy groups were tolerated. All products except **5a** are novel compounds that have not been reported in the literatures.

A reasonable mechanism for the synthesis of **5** is offered in Scheme 2. Apparently, the reaction proceeds by activation of the carbonyl functional group of aldehyde **2** with KCAR (1) for the next addition of enol form of diketone **3** on it to form the corresponding Knoevenagle intermediate **6**. This intermediate is also protonated by KCAR (1) to be activated for the next Michael-type addition reaction with 6-amino-2-thiouracil **4** to afford **7**. Then, cyclization by nucleophilic addition of the amino group to the activated carbonyl group and then dehydration led to the formation of DHP, which is final product **5** (Scheme 2).

CONCLUSION

In conclusion, we have presented an environmentally benign synthetic and one-pot three-component protocol for the synthesis of indeno annulated DHP derivatives in ethanol by the use of KCAR biopolymer as a renewable and heterogeneous catalyst. The present synthetic process with using a green recyclable catalyst based on polysaccharide architecture in order to reduce reaction time and avoiding the use of any transition-metal will be attractive to synthesize polycyclic drug-like structure molecules with functional group diversity.

EXPERIMENTAL SECTION

General. The 6-amino-2-thiouracil, 1,3-indandione, aromatic aldehydes, and solvents used in this work were obtained from Aldrich and Merck chemical Co. Nano TiO_2 (33 nm) from Kemira Co and nano SiO_2 (CAB-O-SIL® M5) was purchased from Cabot Co (60–90 nm). KCAR was commercially available of the best grade and was used without further purification. The NMR spectra were recorded with a Bruker DRX-300 Avance instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C; Bruker Corporation, Germany) with $CDCl_3$ and dimethyl sulfoxide as solvents. Chemical shifts are given in ppm (δ) relative to internal tetramethylsilane, and coupling constant (*J*) are reported in hertz (Hz). Melting points were measured with an electrothermal 9100 apparatus. IR

spectra were measured with Bruker Tensor 27 spectrometer (Bruker Corporation, Ettlingen, Germany). Mass spectra were recorded with an Agilent 5975C VL MSD with triple-axis detector (Agilent Technologies, Santa Clara, CA) operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a PerkinElmer 2004 series [II] CHN elemental analyzer (PerkinElmer, Waltham, MA).

Activation of kappa-carrageenan. In order to optimize KCAR, 1 g of KCAR with 1 mL of 2 M HCl was mixed in a mechanical mortar for 5 min. After filtration, sediment was washed several times with distilled water and methanol to removed unreacted acid and created salt.[11] To increase the contact area of KCAR particles and enhancing its catalytic properties, after drying KCAR in the oven, it will be frozen with liquid nitrogen and grind in satellite mill for 5 h to become very fine particles. Then, the acidity of KCAR was measured by titration with standard solution of NaOH. The obtained amount of acidity for each gram of KCAR was 2.3 mmol. This number is equivalent to the amount of sulfonate groups per gram of carbohydrates.

General procedure for the synthesis of indeno pyrido pyrimidine compounds 4. A mixture of 1,3-indandione (1 mmol, 0.146 g), 4-chlorobenzaldehyde (1 mmol, 0.150 g), 6-amino-2-thiouracil (1 mmol, 0.160 g), and active KCAR (30%, 0.03 g) in ethanol (8 mL) in a 100 mL round-bottomed flask fitted with a reflux condenser was heated with stirring in an oil-bath maintained at 80°C. After complete appearance of the orange solid, the reaction mixture was cooled to room temperature, and resulting solid product was filtered, washed with ethanol, then to separate the catalyst, filtered precipitate rewashed with hot water to removed KCAR.

5-(4-Chloro-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5a). Orange powder: mp = 328–330°C, 0.353 g, yield 90%; IR (KBr) (ν_{max}/cm^{-1}): 3227, 1687, 1602, 1558, 1499, 1411, 1183, 1148, 904, 776, 581; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (1H, s, CH), 7.25–7.32 (6H, m, ArH), 7.37 (1H, t, $^3J_{HH}$ = 7.2 Hz, ArH), 7.48 (1H, t, $^3J_{HH}$ = 7.2 Hz, ArH), 9.85 (1H, s, $NH_.$), 11.64 (1H, s, $NH_.$), 12.38 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8 (CH), 95.4 (**C**═C─N), 109.2 ($C_{ind.}$), 119.2 (CH_{ind}), 121.5 ($CH_{ind.}$), 128.4, 128.6, 130.2, 130.4, 131.1 (Ar), 131.4 ($CH_{ind.}$), 132.7 ($CH_{ind.}$), 132.8 (C_{ind}), 135.9 (C_{ipso} Ar), 143.9 ($C_{ind.}$), 144.8 ($C_{3ind.}$), 153.4 (N═C─N), 160.7 (N─C═O) 174.1 (C═S), 191.1 (C═O); MS (EI, 70 eV): *m*/z (%) = 393 $[M]^+$ (2), 375 (4), 317 (2), 282 (2), 238 (2), 205 (4), 175 (6), 144 (11), 115 (23), 89 (30), 77 (26), 55 (39), 43 (100).

5-(4-Bromo-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5b). Orange powder: mp > 330°C, 0.358 g, yield 82%; IR (KBr) (ν_{max}/cm^{-1}): 3224, 1687, 1602, 1557, 1497, 1404, 1219, 1181, 1145, 903, 775, 580; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.65 (1H, s, CH), 7.21–7.50 (8H, m, ArH), 9.85 (1H, s, $NH_.$), 11.68 (1H, s, $NH_.$), 12.37 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.9 (CH), 95.4 (**C**═C─N), 109.2 ($C_{ind.}$), 119.2 (CH_{ind}), 120.0 ($CH_{ind.}$), 121.5 ($CH_{ind.}$), 130.6, 130.8, 131.4, 131.7, 131.1 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.9 (C_{ipso} Ar), 144.3 ($C_{ind.}$), 144.8 ($C_{3ind.}$), 153.4 (N═C─N), 160.7 (N─C═O) 174.1 (C═S), 191.1 (C═O); MS (EI, 70 eV): *m*/z (%) = 437 $[M]^+$ (6), 384 (31), 356 (15), 327 (9), 298 (21), 274 (37), 246 (33), 189 (55), 150 (21), 104 (89), 76 (100), 55 (53), 43 (24). *Anal*. Calcd (%) for $C_{20}H_{11}BrN_3O_2S$: C, 54.94; H, 2.54; N, 9.61. Found C, 54.6; H, 2.9; N, 9.5.

5-(4-Fluoro-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5c). Orange powder: mp > 330°C, 0.323 g, yield 86%; IR (KBr) (ν_{max}/cm^{-1}): 3231, 1688, 1642, 1602, 1556, 1406, 1221, 1181, 1148, 902, 706, 584; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.69 (1H, s, CH), 7.03 (2H, t, $^3J_{HH}$ = 8.7 Hz, ArH), 7.29 (4H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.36 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.48 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 9.85 (1H, s, $NH_.$), 11.64 (1H, s, $NH_.$), 12.36 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.5 (CH), 95.7 (**C**═C─N), 109.5 ($C_{ind.}$), 115.0, 115.3 (Ar, d, $^2J_{CF}$ = 2 1 Hz), 119.2 ($CH_{ind.}$), 121.5 ($CH_{ind.}$), 130.1, 130.2 (Ar), 131.1 ($CH_{ind.}$), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.9 (C_{ipso} Ar), 141.2 ($C_{ind.}$), 144.7 ($C_{3ind.}$), 146.5 (Ar, d, $^1J_{CF}$ = 275 Hz), 153.0 (N═C─N), 160.8 (N─C═O) 174.0 (C═S), 191.2 (C═O); MS (EI, 70 eV): *m*/z (%) = 375 $[M]^+$ (6), 282 (7), 223 (7), 145.9 (4), 121 (8), 95 (12), 69 (27), 41 (100).

5-(4-Triflluoromethyl-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno[2′,1′:5,6]pyrido [2,3-d]pyrimidine-4,6-dione (5d). Orange powder: mp = 264–266°C, 0.276 g, yield 65%; IR (KBr) (ν_{max}/cm^{-1}): 3231, 1691, 1604, 1555, 1504, 1407, 1326, 1177, 1140, 904, 764, 584; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.8 (1H, s, CH), 7.26–7.60 (8H, m, ArH), 9.93 (1H, s, $NH_.$), 11.70 (1H, s, $NH_.$), 12.38 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.4 (CH), 95.2 (**C**═C─N), 108.9 ($C_{ind.}$), 119.4 (CH_{ind}), 121.6 ($CH_{ind.}$), 125.4 ($CH_{ind.}$), 125.5 (CF_3), 129.0, 129.2, 129.3, 129.5, 131.2 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.8 (C_{ipso} Ar), 145.0 ($C_{ind.}$), 149.4 ($C_{3ind.}$), 153.4 (N═C─N), 160.8 (N─C═O) 174.1 (C═S), 191.1 (C═O); MS (EI, 70 eV): *m*/z (%) = 427 (28) $[M + 1]^+$, 426 (30) $[M]^+$, 425 (100) $[M-2]^+$, 384 (83), 256 (43), 227 (17), 282 (86), 222 (54), 149 (44), 115 (29), 75 (59), 68 (75), 43 (94). *Anal*. Calcd (%) for $C_{20}H_{11}BrN_3O_2S$: C, 59.15; H, 2.60; N, 9.85. Found C, 59.5; H, 2.2; N, 9.7.

5-(4-Methoxy-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5e). Orange powder: mp = 330–332°C, 0.280 g, yield 72%; IR (KBr) (ν_{max}/cm^{-1}): 3225, 1695, 1601, 1558, 1504, 1407, 1286, 1219, 1153, 907, 769, 581; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (3H, s, OMe), 4.62 (1H, s, CH), 7.12–7.53 (8H, m, ArH), 9.82 (1H, s, $NH_.$), 11.65 (1H, s, $NH_.$), 12.29 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.2 (CH), 55.4

(OMe), 96.2 (**C**═C─N), 110.0 ($C_{ind.}$), 113.9, 114.0 (Ar), 119.1 (CH_{ind}), 121.4 ($CH_{ind.}$), 123.4 ($CH_{ind.}$), 129.2, 129.4, 131.0 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.2 (C_{ipso} Ar), 136.2 ($C_{ind.}$), 137.3 ($C_{3ind.}$), 137.5 (N═C─N), 158.3 (N─C═O) 174.1 (C═S), 191.3 (C═O); MS (EI, 70 eV): *m*/z (%) = 388 $[M]^+$ (2), 135 (5), 97 (9), 69 (24), 76 (43), 55 (76), 43 (100), 41 (71). *Anal*. Calcd for $C_{21}H_{14}N_3O_3S$ (388.40): C, 64.93; H, 3.63; N, 10.81. Found: C, 64.5; H, 3.9, N, 10.5.

5-(4-Hydroxy-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5f). Orange powder: mp = 322–323°C, 0.228 g, yield 61%; IR (KBr) (ν_{max}/cm^{-1}): 3412, 3256, 2936, 1690, 1599, 1563, 1507, 1427, 1221, 1181, 1148, 904, 765, 583; ^1H NMR (300 MHz, $CDCl_3$): δ 4.56 (1H, s, CH), 6.59 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.02 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.24–7.28 (2H, m, ArH), 7.35 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.46 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 9.22 (1H, br, OH), 9.77 (1H, s, $NH_.$), 11.64 (1H, s, $NH_.$), 12.31 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.1 (CH), 96.3 (**C**═C─N), 110.3 ($C_{ind.}$), 115.2 (CH_{ind}), 119.0 ($CH_{ind.}$), 121.4 ($CH_{ind.}$), 129.0, 129.2, 129.3, 129.5, 131.0 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.6 (C_{ipso} Ar), 136.1 ($C_{ind.}$), 144.4 ($C_{3ind.}$), 156.4 (N═C─N), 160.8 (N─C═O) 174.0 (C═S), 191.3 (C═O); MS (EI, 70 eV): *m*/z (%) = 375 (4) $[M]^+$, 456 (21), 327 (9), 298 (16), 281 (35), 223 (21), 193 (14), 149 (27), 115 (24), 94 (47), 89 (60), 55 (54), 43 (100). *Anal*. Calcd for $C_{20}H_{12}N_3O_3S$ (374.37): C, 64.16; H, 3.23; N, 11.22. Found: C, 64.5; H, 3.6; N, 11.6.

5-(3-Chloro-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5g). Orange powder: mp = 325–327°C, 0.322 g, yield 82%; IR (KBr) (ν_{max}/cm^{-1}): 3229, 1688, 1602, 1553, 1503, 1399, 1221, 1180, 1151, 903, 771, 573; ^1H NMR (300 MHz, $CDCl_3$): δ 4.69 (1H, s, CH), 7.27 (1H, s, ArH), 7.26 (4H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.36 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 7.47 (1H, t, $^3J_{HH}$ = 7.2 Hz, ArH), 9.89 (1H, s, $NH_.$), 11.70 (1H, s, $NH_.$), 12.30 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.2 (CH), 95.2 (**C**═C─N), 108.9 ($C_{ind.}$), 119.3 (CH_{ind}), 121.5 ($CH_{ind.}$), 126.9 ($CH_{ind.}$), 127.1, 128.2, 130.4, 131.2 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 133.1 (Ar), 135.9 (C_{ipso} Ar), 144.9 ($C_{ind.}$), 147.3 ($C_{3ind.}$), 153.6 (N═C─N), 160.8 (N─C═O) 174.1 (C═S), 191.1 (C═O) MS (EI, 70 eV): *m*/z (%) = 393 (6) $[M]^+$, 384 (100), 356 (48), 298 (47), 274 (28), 246 (23), 189 (34), 149 (55), 104 (46), 76 (66), 43 (80). *Anal*. Calcd for $C_{20}H_{11}ClN_3O_2S$ (392.81): C, 61.14; H, 2.82; N, 10.69. Found: C, 61.5; H, 2.5; N, 10.4.

5-(3-Fluoro-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5h). Orange powder: mp = 331–333°C, 0.330 g, yield 88%; IR (KBr) (ν_{max}/cm^{-1}): 3233, 1691, 1602, 1556, 1498, 1404, 1254, 1216, 1157, 900, 775, 576; ^1H NMR (300 MHz, $CDCl_3$): δ 4.71 (1H, s, CH), 6.95 (1H, t, $^3J_{HH}$ = 9 Hz, ArH), 7.09 (1H, t, $^3J_{HH}$ = 9 Hz, ArH), 7.27 (3H, d, $^3J_{HH}$ = 6 Hz, ArH), 7.39 (1H, t, $^3J_{HH}$ = 9 Hz, ArH), 7.48 (1H, t, $^3J_{HH}$ = 9 Hz, ArH), 9.87 (1H, s, $NH_.$), 11.66 (1H, s, $NH_.$), 12.37 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.1 (CH), 95.3 (**C**═C─N), 109.1 ($C_{ind.}$), 113,6 115.0 (Ar, d, $^2J_{CF}$ = 21 Hz), 119.2 (CH_{ind}), 121.5 ($CH_{ind.}$), 124.4 ($CH_{ind.}$), 130.4, 131.2 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.9 (C_{ipso} Ar), 144.9 ($C_{ind.}$), 146.2 (Ar, d, $^1J_{CF}$ = 250 Hz), 147.8 ($C_{3ind.}$), 153.5 (N═C─N), 160.8 (N─C═O) 174.1 (C═S), 191.1 (C═O); MS (EI, 70 eV): *m*/z (%) = 377 (4) $[M]^+$, 376 (7) $[M\text{-}1]^+$, 375 (15) $[M\text{-}2]^+$, 318 (12), 274 (29), 246 (28), 224 (10), 189 (50), 150 (12), 104 (87), 76 (100), 50 (45). *Anal*. Calcd for $C_{20}H_{11}FN_3O_2S$ (376.36): C, 63.82; H, 2.94; N, 11.16. Found: C, 64.1; H, 2.6; N, 11.4.

5-(2-Hydroxy-4-methoxy-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno[2′,1′:5,6]pyrido [2,3-d]pyrimidine-4,6-dione (5i). Orange powder: mp > 340°C, 0.375 g, yield 93%; IR (KBr) (ν_{max}/cm^{-1}): 3510, 3282, 3196, 1695, 1604, 1554, 1509, 1385, 1185, 1143, 903, 766, 577; ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (3H, s, OMe), 4.71 (1H, s, CH), 6.21–6.28 (2H, m, ArH), 6.93–6.96 (2H, m, ArH), 7.21–7.61 (3H, m, ArH), 9.32 (1H, br, OH), 9.74 (1H, s, $NH_.$), 11.64 (1H, s, $NH_.$), 12.31 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5 (CH), 55.3 (OMe), 95.9 (**C**═C─N), 102.3, 105.1 (Ar), 109.4 ($C_{ind.}$), 118.8 (CH_{ind}), 121.2 ($CH_{ind.}$), 123.5 ($CH_{ind.}$), 130.8, 131.2 (Ar), 132.6 ($CH_{ind.}$), 133.1 ($C_{ind.}$), 136.3 (C_{ipso} Ar), 144.9 ($C_{ind.}$), 153.8 ($C_{3ind.}$), 156.4 (N═C─N), 159.3 (Ar), 161.3 (N─C═O) 173.6 (C═S), 191.2 (C═O); MS (EI, 70 eV): *m*/z (%) = 404 $[M]^+$ (0.5), 402 (4), 274 (13), 211 (6), 181 (8), 155 (6), 129 (11), 92 (31), 83 (44), 69 (87), 58 (100), 43 (96). *Anal*. Calcd for $C_{21}H_{15}N_3O_4S$ (404.39): C, 62.36; H, 3.73; N, 10.39. Found: C, 62.7; H, 3.4; N, 10.7.

5-(2,6-Dichloro-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno [2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5j). Brown powder: mp > 330°C, 0.350 g, yield 82%; IR (KBr) (ν_{max}/cm^{-1}): 3510, 3282, 1695, 1604, 1554, 1509, 1385, 1185, 1143, 903, 766, 577; ^1H NMR (300 MHz, $CDCl_3$): δ 5.65 (1H, s, CH), 7.15–7.54 (7H, m, ArH), 9.96 (1H, s, $NH_.$), 11.74 (1H, s, $NH_.$), 12.32 (1H, s, $NH_.$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.8 (CH), 93.8 (**C**═C─N), 106.3 ($C_{ind.}$), 119.2 (CH_{ind}), 121.3 ($CH_{ind.}$), 128.7, 129.1, 130.2 (Ar), 131.2 ($CH_{ind.}$),132.6 ($CH_{ind.}$), 132.7 ($C_{ind.}$), 134.9 (Ar), 135.7 (C_{ipso} Ar), 136.6 (Ar), 137.0 ($C_{ind.}$), 145.9 ($C_{3ind.}$), 155.1 (N═C─N), 160.2 (N─C═O) 174.0 (C═S), 190.6 (C═O); MS (EI, 70 eV): *m*/z (%) = 427 $[M]^+$ (2), 403 (16), 374 (21), 327 (8), 298 (41), 224 (21), 201 (39), 186 (39), 149.9 (22), 104 (100), 76 (55), 41 (2). *Anal*. Calcd for $C_{20}H_{11}Cl_2N_3O_2S$ (427.26): C, 56.21; H, 2.59; N, 9.83. Found: C, 56.5; H, 2.9; N, 9.6.

5-(2-Chloro-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5k). Orange powder: mp = 320–322°C, 0.348 g, yield 88%; IR (KBr) (ν_{max}/cm^{-1}): 3510, 3253, 1692, 1602, 1546, 1393, 1179, 1139, 899, 771, 577; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09 (1H, s, CH), 7.10–7.50 (8H, m, ArH), 9.89 (1H, s, NH), 11.69 (1H, s, NH), 12.31 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.6 (CH), 95.3 (**C**═C─N), 109.2 ($C_{ind.}$), 119.7 (CH_{ind}), 121.0 ($CH_{ind.}$), 126.5 ($CH_{ind.}$), 126.9, 128.4, 130.0, 131.6 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 133.2 (Ar), 135.7 (C_{ipso} Ar), 144.4 ($C_{ind.}$), 147.6 ($C_{3ind.}$), 153.6 (N═C─N), 160.2 (N─C═O) 174.0 (C═S), 191.3 (C═O); MS (EI, 70 eV): *m*/z (%) = 392 $[M]^+$ (2), 385 (6), 329 (3), 298 (15), 274 (14), 246 (13), 218 (7), 189 (33), 149.9 (8), 104 (56), 76 (100), 41 (13). *Anal*. Calcd for $C_{20}H_{11}ClN_3O_2S$ (392.81): C, 61.14; H, 2.82; N, 10.69. Found: C, 61.4; H, 2.4; N, 10.8.

5-(3-Methoxy-phenyl)-2-thioxo-2,3,5,11-tetrahydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-4,6-dione (5l). Orange powder: mp = 328–330°C, 0.310 g, yield 80%; IR (KBr) (ν_{max}/cm^{-1}): 3506, 3239, 1690, 1602, 1555, 1502, 1402, 1266, 1215, 1157, 906, 772, 576; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (3H, s, OMe),4.64 (1H, s, CH), 6.72 (1H, t, $^3J_{HH}$ = 6 Hz, ArH), 6.80 (2H, d, $^3J_{HH}$ = 6.5 Hz, ArH), 7.14 (1H, t, $^3J_{HH}$ = 8.1 Hz, ArH), 7.27 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.36 (1H, t, $^3J_{HH}$ = 7.2 Hz, ArH), 7.47 (1H, t, $^3J_{HH}$ = 7.2 Hz, ArH), 9.85 (1H, s, NH), 11.67 (1H, s, NH), 12.35 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.1 (CH), 55.4 (OMe), 95.7 (**C**═C─N), 109.6 ($C_{ind.}$), 111.6, 114.7 (Ar), 119.1 (CH_{ind}), 120.4 ($CH_{ind.}$), 121.5 ($CH_{ind.}$), 129.6, 131.0 (Ar), 132.7 ($CH_{ind.}$), 132.8 ($C_{ind.}$), 135.9 (C_{ipso} Ar), 144.7 ($C_{ind.}$), 146.5 ($C_{3ind.}$), 153.3 (N═C─N), 159.5 (Ar), 160.8 (N─C═O) 174.0 (C═S), 191.2 (C═O); MS (EI, 70 eV): *m*/z (%) = 388 $[M]^+$ (0.5), 135 (3), 97 (6), 69 (24), 55 (76), 43 (100), 41 (71). *Anal*. Calcd for $C_{21}H_{14}N_3O_3S$ (388.40): C, 64.93; H 3.63; N 10.81. Found: C, 64.6 H, 3.4 N, 10.7.

4-(4,6-Dioxo-2-thioxo-2,3,4,5,6,11-hexahydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidin-5-yl)-benzoic acid methyl ester (5m). Orange powder: mp = 330–332°C, 0.396 g, yield 95%; IR (KBr) (ν_{max}/cm^{-1}): 3500, 3245, 1690, 1678, 1602, 1552, 1497, 1380, 1245, 1149, 909, 772, 582; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (3H, s, OMe),4.75 (1H, s, CH), 7.26–7.39, 7.46–7.51 (4H, m, ArH), 7.42 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.83 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 9.90 (1H, s, NH), 11.72 (1H, s, NH), 12.38 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5 (CH), 52.5 (OMe), 95.3 (**C**═C─N), 109.0 ($C_{ind.}$), 119.3 (CH_{ind}), 121.5 ($CH_{ind.}$), 128.3, 128.5, 128.8, 129.4, 129.5 (Ar), 131.2 ($CH_{ind.}$), 132.7 ($CH_{ind.}$), 132.8 (C_{ind}), 135.9 (C_{ipso} Ar), 144.9 ($C_{ind.}$), 150.2 ($C_{3ind.}$), 153.6 (N═C─N), 160.7 (N─C═O), 166.6 (MeO─**C**═O), 174.1 (C═S), 191.0 (C═O); MS (EI, 70 eV): *m*/z (%) = 416 $[M]^+$ (3), 385 (6), 357 (5), 298 (10), 246 (7), 218 (4), 189 (26), 150 (7), 104 (74), 76 (100), 59 (51), 50 (49), 41 (12). *Anal*. Calcd for $C_{22}H_{14}N_3O_4S$ (416.40): C, 63.45; H, 3.38; N, 10.09. Found: C, 63.8 H, 3.7; N, 10.3.

REFERENCES AND NOTES

[1] Rostamnia, S.; Xin, H.; Liu, X.; Lamei, K. J Mol Catal A: Chem 2013, 374, 85.

[2] Sheldon, R. A.; Arends, I.; Hanefeld, U. Green Chemistry and Catalysis; Wiley-VCH Verlag GmbH: Weinheim, 2007.

[3] Anastas, P. T.; Kirchhoff, M. M. Acc Chem Res 2002, 35, 686.

[4] Dekamin, M. G.; Azimoshan, M.; Ramezani, L. Green Chem 2013, 15, 811.

[5] Dekamin, M. G.; Eslami, M. Green Chem 2014, 16, 4914.

[6] Varma, R. S. Curr Opin Chem Eng 2012, 1, 123.

[7] Sarma, P.; Saikia, S.; Borah, R. Synth Commun 2015, 45, 2810.

[8] (a) van de Velde, F.; Lourenc, O. N. D.; Pinheiro, H. M.; Bakker, M. Adv Synth Catal 2002, 344, 815; (b) Li, L.; Ni, R.; Shao, Y.; Mao, S. Carbohydr Polym 2014, 103, 1.

[9] Zhao, H.; Zhou, F.; Peng, W.; Zheng, J.; Dziugan, P.; Zhang, B. Food Hydrocoll 2015, 43, 763.

[10] Aldalbahi, A.; Chu, J.; Feng, P. Beilstein J Nanotechnol 2012, 3, 415.

[11] Rostamnia, S.; Doustkhah, E.; Baghban, A.; Zeynizadeh, B. J Appl Polym Sci 2016, 133, 43190.

[12] Mondal, D.; Sharma, M.; Maiti, P.; Prasad, K.; Meena, R.; Siddhanta, A. K.; Bhatt, P.; Ijardar, S.; Mohandas, V. P.; Ghosh, A.; Eswaran, K.; Shah, B. G.; Ghosh, P. K. RSC Adv 2013, 3, 17989.

[13] Campo, V. L.; Kawano, D. F.; da Silva, D. B.; Carvalho, I. Carbohydr Polym 2009, 77, 167.

[14] Mak, C. A.; Ranjbar, S.; Riente, P.; Rodríguez-Escrich, C.; Pericas, M. A. Tetrahedron 2014, 70, 6169.

[15] Rostamnia, S.; Zeynizadeh, B.; Doustkhah, E.; Baghban, A.; Aghbash, K. O. Cat Com 2015, 68, 77.

[16] Baig, R. B. N.; Nadagouda, M. N.; Varma, R. S. Green Chem 2014, 16, 2122.

[17] Lamblin, M.; Nassar-Hardy, L.; Hierso, J. C.; Fouquet, E.; Felpin, F. X. Adv Synth Catal 2010, 352, 33.

[18] Dekamin, M. G.; Ilkhanizadeh, S.; Latifidoost, Z.; Daemi, H.; Karimi, Z.; Barikani, M. RSC Adv 2014, 4, 56658.

[19] Daştan, A.; Kulkarni, A.; Török, B. Green Chem 2012, 14, 17.

[20] Astwood, E. B. J Pharm Exp Ther 1943, 78, 79.

[21] Wamhoff, H.; Dzenis, J.; Hirota, K. Adv Heterocycl Chem 1992, 55, 129.

[22] Nogimori, T.; Emerson, C. H.; Braverman, L. E.; Wu, C. F.; Gambino, J.; Wright, G. E. J Med Chem 1985, 28, 1692.

[23] Brown, D. J.; Katritzky, A. R.; Rees, C. W. In Comprehensive Heterocyclic Chemistry; McKillop, B. Ed.; Elsevier: Amsterdam, 1984; Vol 3, p. 150.

[24] Agrawal, A.; Chauhan, P. M. S. Tetrahedron Lett 2005, 46, 1345.

[25] Swaminathan, S.; Chacko, K. K. Acta Crystallogr Sect B 1978, 34, 3108.

[26] Mohamed, N. R.; El-Saidi, M. M. T.; Ali, Y. M.; Elnagdi, M. H. Bioorg Med Chem 2007, 15, 6227.

[27] Chebanov, V. A.; Saraev, V. E.; Gura, E. A.; Desenko, S. M.; Musatov, V. I. Chem Plus Chem 2005, 70, 350.

[28] Gangjee, A.; Aldair, O.; Queener, S. F. J Med Chem 1999, 42, 2447.

[29] Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. J Med Chem 1980, 23, 327.

[30] Furuja, S.; Ohtaki, T. Eur Patent Appl EP 608565 1994 [Chem Abstr 1994, 121, 205395].

[31] Heber, D.; Heers, C.; Ravens, U. Pharmazie 1993, 48, 537.

[32] Sakuma, Y.; Hasegawa, M.; Kataoka, K.; Hoshina, K.; Yamazaki, N.; Kadota. T.; Yamaguchi, H. US Patent 5,661,148, 1997. Washington DC

[33] Singh, G.; Singh, G.; Yadav, A. K.; Mishraa, K. Indian J Chem B 2002, 41, 430.

[34] Zakharov, A. V. Farm Zh 1994, 28, 24.

[35] DeGraw, J. I.; Christie, P. H.; Clowell, W. T.; Sirotnak, F. M. J Med Chem 1992, 35, 320.

[36] Wang, X. S.; Zeng, Z. S.; Shi, D. Q.; Wei, X. Y.; Zong, Z. M. Synth Commun 2004, 34, 4331.

[37] Narayana, B. L.; Rao, A. R. R.; Rao, P. S. Eur J Med Chem 2009, 44, 1369.

[38] El-Gazzar, A. B. A.; Hafez, H. N. Bioorg Med Chem Lett 2009, 19, 3392.

[39] Ahluwalia, V. K.; Batla, R.; Khurana, A.; Kumar, R. J Chem 1991 22.

[40] Kots, A. Y.; Choi, B. K.; Estrella-Jimenez, M. E.; Warren, C. A.; Gilbertson, S. R.; Guerrant, R. L.; Murad, F. Proc Natl Acad Sci 2008, 105, 8440.

[41] Rizkalla, B. H.; Broom, A. D. J J Org Chem 1972, 37, 3980.

[42] Wamhoff, H. I.; Katritzky, A. R.; Rees, C. W. In Comprehensive Heterocyclic ChemistryKatritzky, A. R.; Rees, C. W. Eds.; Academic Press: New York, 1984; Vol 5, p. 669.

[43] Tamura, G.; Sakaguchi, T.; Kawasaki, T.; Kita, Y. Heterocycles 1975, 3, 183.

[44] Quiroga, J.; Hormaza, A.; Insuasty, B.; Nogueras, M.; Sa'nchez, A.; Hanold, N.; Meier, H. J Heterocycl Chem 1997, 34, 521.

[45] Hirota, K.; Kuki, H.; Maki, Y. Heterocycles 1994, 37, 563.

[46] Srivastava, P.; Saxena, A. S.; Ram, V. J Synthesis 2000, 2000, 541.

[47] Broom, A. D.; Shim, J. L.; Anderson, G. L. J Org Chem 1976, 41, 1095.

[48] Mohamed, N. R.; Elsaidi, M. M.; Ali, Y. M.; Elnagdi, M. H. Bioorg Med Chem 2007, 15, 6227.

[49] Devi, I.; Kumar, B. S. D.; Bhuyan, P. J. Tetrahedron Lett 2003, 44, 8307.

[50] Quiroga, J.; Insuasty, H.; Insuasty, B.; Abonia, R.; Cobo, J.; Sa'nchez, A.; Nogueras, M. Tetrahedron 2002, 58, 4873.

[51] El-Shafei, A.; Fadda, A. A.; Bondock, S.; Khalil, A. M.; Tawfik, E. H. Synth Commun 2010, 40, 2788.

[52] Hassaneen, H. M. ARKIVOC, 2007, (i), 154.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.