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An efficient protocol for the synthesis of tetrahydropyrimidine-5-carboxamides: $La(NO_3)_3.6H_2O$ as a convenient catalyst for Biginelli-type reaction under the solvent-free condition

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Abstract: In this paper**,** a simple and highly efficient protocol for the synthesis of tetrahydropyrimidine-5-carboxamide has been reported using$La(NO_3)_3.6H_2O$ as catalyst under solvent-free conditionat 80°C. This method offers several advantages such as short reaction times, no waste formation,eco-friendliness, simple purification steps and high yield. In this work, six derivatives of pyrimidinone have been synthesized for the first time. These newly synthesized derivatives were characterized by ^{1}HNMR and ^{13}CNMR techniques.

Keywords: Biginelli-type reaction, Tetrahydropyrimidine-5-carboxamide, $La(NO_3)_3.6H_2O$, Solvent-free.

Introduction

In recent years, the chemistry of heterocyclic compounds has attracted much more attention due to their great importance in fields such as medical and material sciences, as the majority of biologically active drugs and agrochemicals contain a heterocyclic segment. Among the approximately 20 million recognized chemical compounds, more than two-thirds of aromatic compounds and about half of compounds are heterocyclic [1]. The synthesis of Heterocyclic rings has broad health benefits such as anti-tuberculosis, anti-fungal, anti-AIDS, anti-malarial, anti-tumor, hypnotics, anticonvulsants, and antidepressants[2-8]. Heterocyclic compounds are included nitrogen heteroatoms, sulfur [1], oxygen [9], phosphorus [10] and selenium [11].

Among them, heteroatoms of nitrogen and oxygen have attracted more interest of researchers for organic synthesis.

They have been found in a large number of naturally-occurring medicinal and pharmaceutical compounds such as papaverine, theobromine, metronidazole, methotrexate and chlorpromazine (Figure 1) [12-16].

Multi-component reactions (MCRs) have received great attention in organic chemistry as a powerful tool for the synthesis of complex molecules as well as their utility in drug discovery processes [17-21]. Multicomponent reactions act as one-potones [22]. Since the first report on multi-component reactions by Laurent and Gerhardt in 1838 [23], their usability in design and synthesisof heterocyclic compounds has been regarded by researchers [24-30], due to a variety of advantages such as reducing response times, decreasing byproducts, atom economy, high efficiency as well as high selectivity [31,32].

Dihydropyrimidineanalogues, recognized as an important category of six-membered nitrogen-containing heterocyclic compounds possessing two nitrogen heteroatoms, have caused concern because of

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their medicinal and biological properties. The applicability of dihydropyrimidines and their analogues as antibacterial [33], antitumor [34,35], anti-inflammatory [36], anti-virus [37], anti-hypertensive[38] and anti-pain [39] as well as anti-AIDS [40,41] have been proven in the literature. Furtheremore, heterocyclic compounds with a pyrimidinone (thione) core have shown to possess many medicinal properties [42].

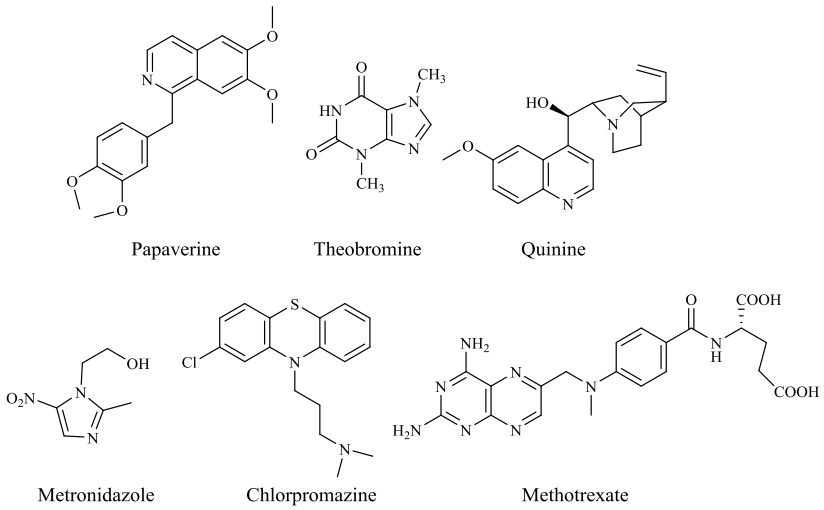


Figure 1: Natural and synthetic heterocyclic compounds with medicinal properties

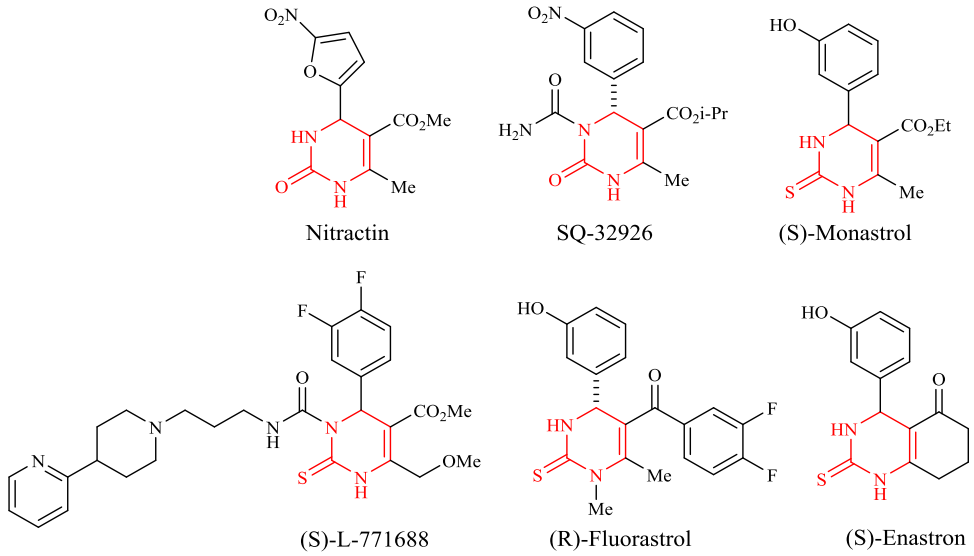


Figure 2: Pharmaceutical compositions containing Pyrimidinone (thione) rings

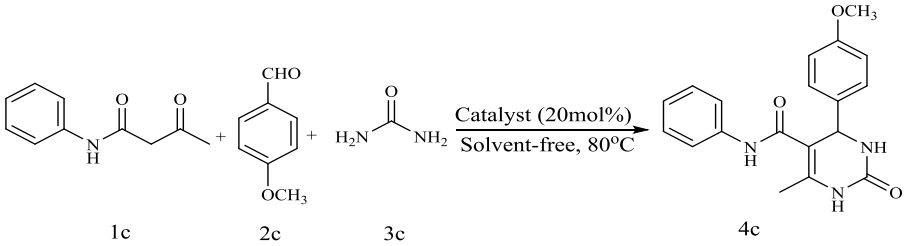
The first report on the synthesis of dihydropyrimidines between ethyl acetoacetate, aldehyde aromatic, and urea was presented by Pietro Biginelli in 1893, known as, in his honor, the Biginelli reaction [43]. Since that time, a wide variety of modifications have been provided for the classical Biginelli reaction employing novel reactants in the presence of new and efficient catalysts. In recent years, scholarly interest in these compounds has been increased because Biginelli compound shows a wide variety of biologically active compounds [44,45]. Nitractin is a biologically active compound that has

anti-viral activity [46,47]. In recent years, synthesis of 3,4-dihydropyrimidines has been achieved in the presence of a variety of catalysts such as $InCl_3$[48], $Mn(OAc)_3$[49], AcOH [50], H_2SO_4[51], $LaCl_3$[52], KSF.Clay[53], $LiClO_4$[54], $CdCl_2$[55], $InBr_3$[56], $BF_3.OEt_2$[57], $SiO_2/NHSO_4$[58], LiBr[59], $Cu(OAc)_2$[60], $AlCl_3.H_2O$[61], $ZrCl_4$[62], $FeCl_3$[63], ceric ammonium nitrate (CAN)[64], *P*-TSA[65] and microwave [66,67]. Nevertheless, a few reports on the use of acetoacetanilide in Biginelli reaction have been published [69-73].

In recently years, lanthanides were reported as efficient catalysts in modern synthetic organic chemistry[74-77].In line with our interest in multicomponent reactions [78-82], in order to modify previous procedures and remove their difficulties in the current study, an efficient and appropriate way for the preparation of tetrahydropyromidine-5-carboxamide derivatives via a Biginelli-type reaction has been attained.

Results and discussion

At the beginning of this work, the one-pot three-component reaction betweenacetoacetanilide, 4-methoxybenzaldehydeand urea was chosen as a model reaction at a ratio of 1: 1: 1.2 (mmol) in the presence of different catalysts at 80 °C under solvent-free condition (scheme **1**).In the absence catalyst, no product was formed after 48 hour, which indicated that the catalyst's presence is necessary for this reaction (Table **1**, entry 1).The reaction was carried out in the presence of various catalysts, but the tetrahydropyrimidine-5-carboxamide was produced in higher yield in the presence La $(NO_3)_3.6H_2O$ (Table **1**, entry 2-6). For optimizing the reaction conditions, the reaction between 4-methoxybenzaldehyde, acetoacetanilideand urea was investigated under different temperature and solvent. The results are summarized in Table **2**.



Scheme 1: Reaction between acetoacetanilide (1mmol), 4-methoxybenzaldehyde (1mmol) and ur

Table1: The effect of different catalysts on synthesis of Tetrahydropyrimidine-5-carboxamide

Entry	Catalyst (20 mol%)	Reaction time (min)	Isolated Yields (%)
1	none	48h	-
2	$Cr(NO_3)_3.9H_2O$	60	Trace
3	$Bi(NO_3)_2.5H_2O$	60	63
4	$La(NO_3)_3.6H_2O$	13	90
5	$CdCl_2.6H_2O$	60	35
6	Oxalic acid	60	45

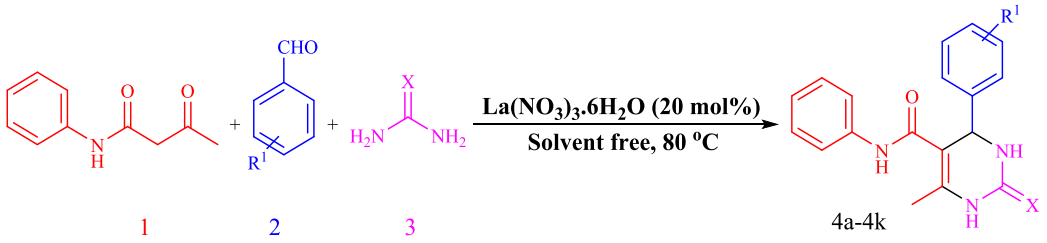
At first, the model reaction was studied at different temperatures. At the ambient temperature, the reaction proceeds very low. The yield improved as temperature was increased, and the best efficiency was observed at 80 ° C. On the other hand, amount of catalyst were studied and the best result was observed for 20mol%. Furtheremore, the role

of solvent was assayed. Surprisingly, the best result obtained under solvent-free condition (Table **2**).

Table 2: Optimization of the reaction conditions for the synthesis of tetrahydropyrimidine-5-carboxamide

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Isolated Yields (%)
1	None	-	80	48h	-
2	5	-	80	10	38
3	10	-	80	12	40
4	15	-	80	11	40
5	20	-	80	13	90
6	20	-	r.t.	24h	Trace
7	20	-	60	15	48
8	20	-	90	15	60
9	20	-	100	15	60
10	20	EtOH	Reflux	24h	Trace
11	20	H_2O	80	24h	Trace
12	20	EtOH/H_2O (1:1)	80	24h	Trace

To show universality of the method, various aromatic aldehydes were applied and the results are summarized inTable **3**.According to the obtained data, a wide variety of aromatic aldehydes possessing electron-donating, electron-withdrawing and multi-substituted afforded the corresponding products in high go excellent yields.



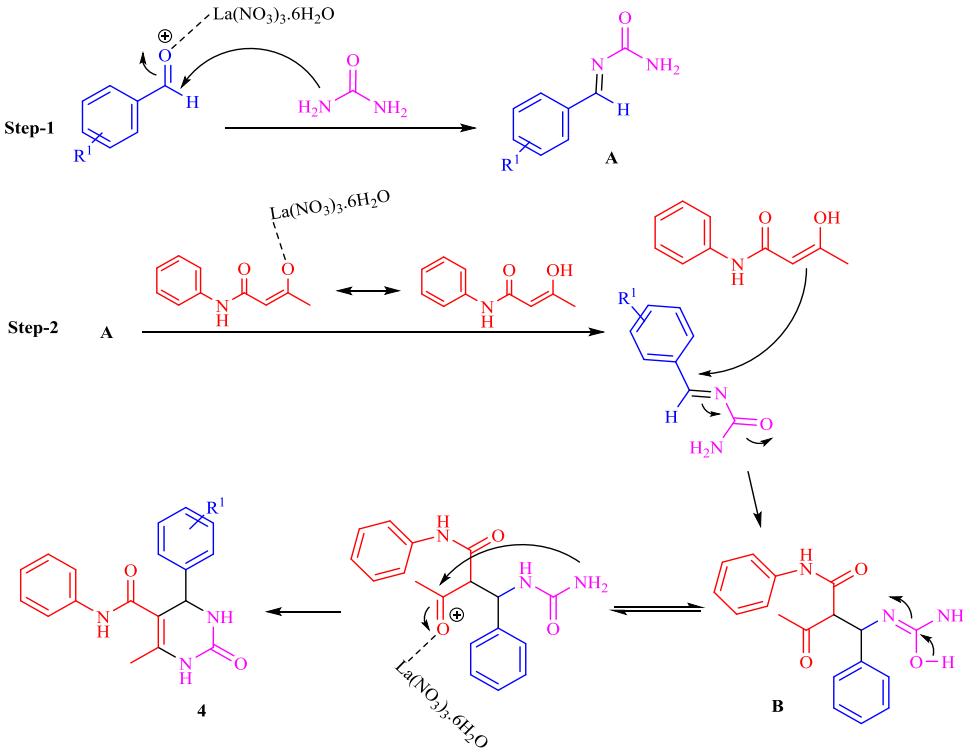
Scheme 2: Three-component synthesis of tetrahydropyrimidine-5-carboxamide derivatives

Table 3: Synthesis of tetrahydropyrimidine-5-carboxamide derivatives

Entry	R^1	X	Product	Time(min)	Isolated Yield(%)	Obtained M.P. (°C)	M.P. (°C)/[ref]
1	H	O	4a	13	94	245-247	239-240[69]
2	H	S	4b	23	90	218-220	214-217[70]
3	4-OMe	O	4c	13	90	237-239	240-242[69]
4	4-Cl	O	4d	30	92	248-250	245-247[69]
5	4-CN	O	4e	35	93	263-265	268-271[69]
6	3-OH	O	4f	17	87	259-260	262-263[69]
7	4-OH	O	4g	24	89	280-283	286-288[69]

8	2-Thiophene	O	4h	30	85	180-182	174-178[71]
9	4-Me	O	4i	15	89	250-252	254-256[69]
10	4-Me	S	4j	25	85	179-181	This work
11	3,4,5-triOMe	O	4k	12	88	224-226	This work
12	3,4,5-triOMe	S	4l	20	85	256-258	This work
13	2-OH-3-OMe	O	4m	12	88	252-255	This work
14	2-OH-3-OMe	S	4n	17	85	246-248	This work
15	4-NHAc	O	4o	23	85	264-266	This work

Based on the proposed mechanism [69, 70], intialBiginelli condensation reaction starts through the formation of acyliminium ion intermediate (A) via coordination $La(NO_3)_3.6H_2O$ as a Lewis acid with carbonyl groups, then intermediate A generated by the loss water. In the next step, the addition of the acyliminium ion to acetoacetanilide produced intermediate B, which after cyclization and dehydration A and B intermediatesleads to obtaining tetrahydropyrimidine-5-carboxamid(4). The proposed mechanismis presented in scheme **3**.



Scheme 3: Proposed mechanism for the synthesis of tetrahydropyrimidine-5-carboxamide

Conclusion

This paper introduce a one-pot three-component reaction for synthesizing of tetrahydropyrimidine-5-carboxamide using La $(NO_3)_3.6H_2O$ as catalyst. In this research, 15 derivative of tetrahydropyrimidine-5-carboxamide have been produced. The new synthesized derivatives were proved using ^{1}HNMR and ^{13}CNMR techniques. This method has several advantages including short reaction time, solvent-free condition, no waste formation, eco-friendliness and satisfactory yields of products, as well as a simple isolation and purification of the products that make it a

useful protocol for the synthesisof pyrimidine-5-carboxamides.

Experimental

General

All reagents were purchased from Merck (Darmstadt, Germany), Acros (Geel, Belgium) and were used without further purification. Melting points were measured on an electrothermal 9100 apparatus. The ^{1}H NMR and ^{13}CNMR spectra were recorded on a Bruker DRX-300 avance instrument.

General procedure for the synthesis of tetrahydropyrimidine-5-carboxamide (4a-4o):

A Solution of acetoacetanilide**1** (1mmol), aromatic aldehyde **2** (1mmol) and urea or thiourea**3** (1.2mmol) in the presence of $La(NO_3)_3.6H_2O$ (20mol%) at 80 ° C was stirred for the appropriate time. After the completion of reaction, determined through thin-layer chromatography (TLC) monitoring and using ethyl acetate/*n*-hexane (2:7) as the solvent for TLC.The reaction mixture was cooled to room temperature. The thick precipitate was collected with water and was filtered off through a funnel, the resulting crude product was recrystallized using hot EtOH to obtain pure product. Physical and spectral data for selected products are represented as follows.

4-(4-methoxyphenyl)-6-methyl-2-oxo-N-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4c):

^{1}H NMR (300 MHz, DMSO):δ = 2.06(3H,s), 3.71(3H,s), 5.38(1H, d, *J*=1.8Hz), 6.88(2H, d, *J*=8.7Hz), 7.00(1H, t, *J*=14.7, 7.2Hz), 7.24(4H, dd, *J*=15.6, 7.8Hz), 7.56(3H, d, *J*=14.7, 7.2Hz), 8.72(1H, d, *J*=0.9Hz), 9.54(1H,s) ppm.

6-methyl-2-oxo-N-phenyl-4-(p-tolyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4i):

^{1}H NMR (300 MHz, DMSO):δ = 2.04(3H, s), 2.26(3H, s), 5.38(1H, d, *J*= 2.4Hz), 7(1H, t, *J*= 14.4, 7.2Hz), 7.17(4H, dd, *J*= 13.5, 5.4Hz), 7.27(2H, t, *J*= 7.5, 1.8Hz), 7.54(1H, s), 7.57(2H, t, *J*= 3.3, 1.2Hz), 8.70(1H, d, *J*= 1.5Hz), 9.54(1H, s)ppm. ^{13}C NMR (300MHz, DMSO): δ = 17.5, 21.1, 55.3, 106.0, 120.0, 123.5, 126.6, 128.9, 129.4, 136.9, 138.6, 139.7, 141.8, 153.0, 165.8ppm.

6-methyl-N-phenyl-2-thio-4-(*p*-tolyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4j):

^{1}H NMR (300 MHz, DMSO):δ = 2.07(3H, s), 2.27(3H, s), 5.38(1H, d, *J*= 2.4Hz), 7.03(1H, t, *J*= 14.7, 7.2Hz), 7.16(4H, s), 7.27(2H, t, *J*= 15.9,7.5Hz), 7.56(2H, d, *J*= 7.5Hz), 9.42(1H, s), 9.73(1H, s), 9.98(1H, s) ppm.^{13}C NMR (300MHz, DMSO): δ = 16.9, 21.1, 55.3, 107.8, 120.1, 123.8, 126.8, 129.0, 129.6, 135.7, 137.4, 139.4, 140.6, 165.4, 174.4 ppm.

6-methyl-2-oxo-N-phenyl-4-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4k):

^{1}H NMR (300 MHz, DMSO):δ = 2.04(3H, s), 3.36(3H, s), 3.65(3H, d, *J*= 22.8Hz), 6.58(2H, s), 7.02(1H, t, *J*= 14.7, 7.5Hz), 7.27(2H, t, *J*= 15.6, 7.5Hz), 7.57(3H, t, *J*= 7.2, 3.3Hz), 8.73(1H, d, *J*= 1.2Hz), 9.63(1H, s)ppm. ^{13}C NMR (300MHz, DMSO): δ = 17.5, 55.5, 56.2, 103.8, 105.6, 120.0, 123.6, 129.0, 137.1, 138.6, 139.6, 140.2, 153.0, 153.3, 160.0, 166.0ppm.

6-methyl -N-phenyl-2-thio-4-(3, 4, 5 trimethoxyphenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4l):

^{1}H NMR (300 MHz, DMSO):δ = 2.07(3H, s), 3.63(3H, s), 3.70(6H, s), 5.38(1H, d, *J*= 2.1Hz), 6.58(2H, s), 7.04(1H, t, *J*= 14.7, 7.2Hz), 7.29(2H, t, *J*= 15.6, 7.5Hz), 7.57(2H, d, *J*= 7.5Hz), 9.41(1H, s), 9.81(1H, s), 10.02(1H, s) ppm.^{13}C NMR (300MHz, DMSO): δ = 16.9, 55.5, 56.2, 60.4, 103.9, 107.6, 120.2, 123.9, 129.0, 135.8, 137.4, 138.9, 139.4, 153.4, 165.6, 174.7 ppm.

4-(2-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-N-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4m):

^{1}H NMR (300 MHz, DMSO):δ = 1.75(3H, s), 3.18(1H. s), 3.75(3H, s), 4.52(1H, q, *J*= 5.1, 2.4Hz), 6.78(1H, dd, *J*= 9.3,2.7Hz), 6.85-6.91(2H, m), 7.06(1H, t, *J*= 14.7, 7.5Hz), 7.14(1H, d, *J*= 3.9Hz), 7.33(2H, t, *J*= 15.9, 7.8Hz), 7.49(1H, s), 7.60(2H, d, *J*= 7.5Hz), 10.18(1H, s) ppm. ^{13}C NMR (300MHz, DMSO): δ = 24.1, 45.0, 49.0, 55.8, 83.9, 111.9, 119.4, 120.5, 120.6, 123.7, 127.1, 129.2, 139.5, 140.6, 148.6, 155.1, 167.3ppm.

4-(2-hydroxy-3-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4n):

^{1}H NMR (300 MHz, DMSO):δ = 1.80(1H, s), 3.21(1H, s), 3.77(3H, s), 4.64(1H, q, *J*= 4.8, 2.7Hz), 6.79(1H. dd, *J*= 6.3, 2.7Hz), 6.87-6.96(2H, m), 7.08(1H, t, *J*=14.7, 7.2Hz), 7.33(2H, t, *J*=15.9, 7.8Hz), 7.59(2H, d, *J*=7.5Hz), 9.04(2H, t, *J*= 11.4, 6.3Hz), 10.20(1H, s)ppm.^{13}C NMR (300MHz, DMSO): δ = 23.4, 43.3, 49.5, 55.8, 82.1, 112.3, 119.4, 119.6, 120.6, 121.0, 123.9, 125.5, 129.3, 139.3, 140.3, 148.5, 166.6, 176.8 ppm.

4-(4-acetamidophenyl)-6-methyl-2-oxo-N-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (4o):

^{1}H NMR (300MHz, DMSO): δ = 2.01(3H, s), 2.04(3H, s), 5.36(1H, d, *J*= 1.5Hz), 7(1H, t, *J*= 14.7, 7.5Hz), 7.18-7.27(4H, m), 7.53(5H, dd, *J*= 10.8, 7.5Hz), 8.71(1H, s), 9.53(1H, s), 9.92(1H, s) ppm. ^{13}C NMR (300MHz, DMSO): δ = 17.5, 24.4, 55.2, 105.9, 119.5, 120.0, 123.5, 127.1, 128.9, 138.5, 138.9, 139.3, 139.6, 152.9, 165.8, 168.6ppm.

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