Synthesis, Characterization and Application Studies of 3-Methylbenzoyl Thiourea Derivatives as Organocatalysts

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Two new carbonyl thiourea derivatives, 3-methyl-*N*-((3,3,5-trimethyl-5-((3-(3-methylbenzoyl) thioureido)methyl)cyclohexyl)carbamothioyl)benzamide (**3-MBTC**) and *N*-(3-methylbenzoyl)-*N'*-(4-aminobutyl)thiourea (**3-MBTB**) were successfully synthesized. These compounds were characterized using Fourier Transform Infra-Red, Nuclear Magnetic Resonance (^{1}H & ^{13}C), Micro elemental analysis, and Mass spectroscopy. The infrared spectra of these compounds showed four significant stretching vibrations, *v*(N-H), *v*(C=O), *v*(C-N), and *v*(C=S) at 3256-3235 cm^{-1}, 1667-1663 cm^{-1}, 1157-1152 cm^{-1}, and 743-740 cm^{-1}, respectively. Proton NMR spectra showed the expected resonances of (C=S-NH) and (C=O-NH) appeared in the range of δ_H 10.83-11.19 ppm and 11.19-11.30 ppm, respectively. Meanwhile, carbon NMR spectra showed the expected resonances of (C=O) and (C=S) appeared in δ_C 166-168 ppm and δ_C 179-180 ppm. These compounds were tested as organocatalysts in the Michael addition reaction of *N*-phenylmaleimide and isobutyraldehyde. The performance of the synthesized compounds as organocatalysts was monitored using Gas Chromatography-Flame Ionization Detector (GC-FID). Under optimum conditions, catalyst **3-MBTC** gave 72% of yield, while **3-MBTB** gave 76% of yield. Both of the synthesized compounds could act as ideal potential catalysts in Michael addition reaction.

Key words: Organocatalyst; thiourea; Michael addition; *N*-phenylmaleimide; isobutyraldehyde

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Organocatalysts have been paid much attention in the design and application of asymmetric synthesis in order to produce valuable synthetic building blocks [1, 2]. Organocatalysts become attractive due to the absence of transition metals and also give an advantage to prepare compounds that do not tolerate metal contamination, such as pharmaceutical products [3]. Recently, non-covalent organocatalysts such as thiourea and thiol have been mainly developed as hydrogen bond or proton donors [4].

In organic synthesis, Michael addition reaction is one of the most efficient carbon-carbon bond formation reaction [5, 6, 7]. To date, organocatalysts are widely applied in asymmetric Michael addition of maleimides and isobutyraldehyde in order to produce substituted succinimides. Substituted succinimides are usually used as intermediates in the synthesis of natural products and some clinical drugs [8, 9]. Besides, substituted succinimides are also used as chiral building blocks or precursors of biologically active compounds [1, 2].

The organocatalytic asymmetric Michael addition of maleimides and isobutyraldehyde was pioneered by [10] using α,α-phenylprolinol silyl ether as a catalyst but lower yield was observed. As a result, considerable effort has been directed towards the development of an organocatalytic asymmetric of the Michael addition of maleimides and isobutyraldehyde. Over recent years, many improvements to this reaction have been made especially the use of thiourea-based catalysts instead of α,α-phenylprolinol silyl ether. The ability of thiourea derivatives to serves as organocatalysts was recently recognized by [11] that gave a highly efficient conjugate addition reaction of isobutyraldehyde with maleimides. Thiourea has been widely used as an organocatalyst due to the ability to form an extensive network of hydrogen bonds because it possesses a large dipole moment [12]. In this study, with an interest in developing an efficient organocatalytic system to achieve high levels of yield in Michael addition reaction of maleimides and isobutyraldehyde, we have designed a new organic catalyst that possessed a thiourea moiety.

METHODOLOGY

All chemicals or reagents used were purchased from standard commercial suppliers (Fisher Scientific, Merck, and Sigma Aldrich) and used as received without further purification. FTIR of the synthesized compounds was recorded between 4000 and 400 cm^{-1} as potassium bromide (KBr) pellets on Perkin Elmer Spectrum 100. CHNS elemental analysis was used to determine the percentage of C, H, N, and S in the synthesized compounds. The values of CHNS elemental analysis for each sample were resolved

using FlashEA 1112 series CHNS analyzer. NMR spectroscopy was used to identify and elucidate the structures of the synthesized compounds. ^{1}H and ^{13}C-NMR of the synthesized compounds were recorded using Bruker Avance III 400 spectrometer in deuterated dimethyl sulfoxide (DMSO- d_6) and deuterated chloroform ($CDCl_3$). Mass spectrometry (MS) of the synthesized compounds was recorded using gas chromatography mass spectrometer GCMS-QP2010 Ultra. The ionizing source used was electron impact ionization (EI). All MS samples were prepared by dissolving them in acetone. The performance of catalytic activities of the synthesized compounds was carried out using Shidmadzu GC2010 Plus. Samples were analyzed with a 30 m × 0.25 mm × 0.25 µm universal capillary column (BPX5, 95% methyl polysilphenylene) using flame ionization detector (FID). FID detector is useful as a general detector for the analysis of organic compounds and also has high sensitivity.

Synthesis Method

3-methylbenzoyl thiourea derivatives were prepared according to the method reported by [13] with minor modifications. Figure 1 shows the chemical structure of 3-MBTB and 3-MBTC.

3-methyl-N-((3,3,5-trimethyl-5-((3-(3-methylbenzoyl) thioureido)methyl)cyclohexyl) carbamothioyl) benzamide (3-MBTC)

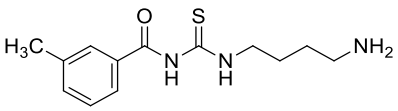
A solution of ammonium thiocyanate (20.00 mmol) in acetone (30 mL) was added dropwise into *m*-tolouyl chloride (20.00 mmol) solution which was dissolved separately in 30 mL of acetone. The mixture was stirred at room temperature for 10 minutes. A solution of isophoronediamine (10.00 mmol) in 30 mL of acetone was then added into the reaction mixture. The mixture was stirred and refluxed for around 1 hours. The resulting solution was filtered into a beaker containing ice cubes. The solid product formed was then recrystallized by methanol to give colorless crystals. Yield 57 %; IR (KBr pellets): (N-H) 3239 cm^{-1}, (C=O) 1664 cm^{-1}, (C-N) 1321 cm^{-1}, (C=S) 745 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400.11 MHz): δ 0.94-1.26 (m, 18H, $C_{10}H_{18}$); 2.35, 2.37 (s, 6H, 2 × CH_3); 7.37- 7.80 (m, 8H, 2 × C_6H_4); 10.83, 11.19 (m, 2H, 2 × NH-R); 11.27, 11.30 (s, 2H, 2 × NH). ^{13}C NMR (DMSO-d_6, 100.61 MHz): δ 20.7- 27.3 (CH_3); 29.7- 48.3 (C_6H_7); 125.7 – 137.8 (2 × Ar C); 168.4, 168.6 (2 × C=O); 179.0, 180.9 (2 × C=S).

N-(3-methylbenzoyl)-N'-(4-aminobutyl)thiourea (3-MBTB)

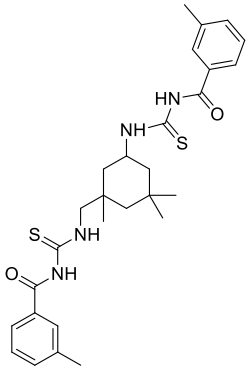
In the preparation of 3-MBTB, *m*-toluoyl chloride (20.00 mmol), ammonium thiocyanate (20.00 mmol), and 1,4-diaminobutane (10.00 mmol) were used. The synthesis method for 3-MBDB was the same as described in the preparation of 3-MBTC. The solid product formed was then recrystallized by methanol to give colorless crystals. Yield 95 %; IR (KBr pellets): (N-H) 3300 cm^{-1}, (C=O) 1632 cm^{-1}, (C-N) 1315 cm^{-1}, (C=S) 746 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400.11 MHz): δ 1.47-1.70 (m, 4H, 2× CH_2); 2.37 (s, 3H, CH_3); 3.62-3.68 (m, 4H, 2× CH_2); 7.37-7.76 (m, 4H, C_6H_4); 10.91 (m, 1H, NH-R); 11.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100.61 MHz): δ 21.0, 25.2, 26.6, 44.5 (CH_2); 20.9 (CH_3); 127.1, 128.5, 128.8, 129.0, 129.2, 131.7 (Ar C); 166.3 (C=O); 180.0 (C=S).

Catalytic Performance of 3-MBTC and 3-MBTB as Organocatalysts

The efficiency of **3-MBTC** and **3-MBTB** as organo-catalysts was tested in Michael reaction of iso-butyraldehyde and *N*-phenylmaleimide. The catalytic performance was monitored by GC-FID and was also determined by the percentage conversion of the



3-MBTB



3-MBTC

Figure 1. Chemical structure of 3-MBTB and 3-MBTC

limiting reactant, which was *N*-phenylmaleimide into the product. Percentage (%) conversion was calculated using the following equation:

$$\% \text{ conversion} = \frac{(\text{A initial of } N\text{−phenylmaleimide}) - (\text{A final of } N\text{−phenylmaleimide})}{\text{A initial of } N\text{−phenylmaleimide}} \text{ x } 100$$

$A_{initial}$ = peak area of *N*-phenylmaleimide before reaction
A_{final} = peak area of *N*-phenylmaleimide after reaction

The preparation for the catalytic study was based on the work by [5] with minor modifications. In this study, the solution of **3-MBTC** (0.04 mmol) in 1 mL of dichloromethane was added with isobutyraldehyde (0.4 mmol) and *N*-phenylmaleimide (0.2 mmol). The mixture was stirred at room temperature for 6 hours. After stirring, the mixture was injected into the injection port of GC-FID to resolve the performance of catalytic activities. The above steps were repeated using **3-MBTB** as the organocatalyst.

RESULTS AND DISCUSSION

FTIR Spectroscopy

IR spectra of 3-MBTB and 3-MBTC showed all the expected bands of interest namely ν(N-H),ν(C=O),ν(C-N), and ν(C=S). The first absorption band for 3-MBTB was assigned as primary amine which could be observed at 3256 cm^{-1}. Meanwhile, the first absorption band for 3-MBTC was assigned as secondary amine which could be observed at 3235 cm^{-1}. Both of these absorption bands were observed in medium intensity. Usually primary amine would consist of two N-H stretching which represent the symmetric and asymmetric stretching of the N–H bonds but in 3-MBTB only a single peak was observed, probably due to the overlapping between symmetric and asymmetric stretching of the N-H bonds. The strong absorption of ν(C=O) stretching band was observed at 1663 cm^{-1} (3-MBTB) and 1667 cm^{-1} (3-MBTC) which deviated from ordinary ν(C=O) stretching band, which is commonly observed at around 1700 cm^{-1} due to the presence of intramolecular hydrogen bond, C=O·····H-N and resonance effect of nitrogen and carbonyl group [13]. Strong absorption of ν(C-N) absorption band was clearly observed at 1157 cm^{-1} and 1152 cm^{-1}. ν(C=S) could be observed at 740 cm^{-1} (3-MBTB) and 743 cm^{-1} (3-MBTC), apparently decreased in frequency compared to common vibration due to the formation of intramolecular hydrogen bond between C=O and N-H that caused the electronegativity property of NH group to became stronger and increased the strength of double bond character of the C=S group and restricted the thioamides resonance [14]. Figure 2 shows the IR spectrum of **3-MBTB** and Figure 3 shows the IR spectrum **of 3-MBTC**.

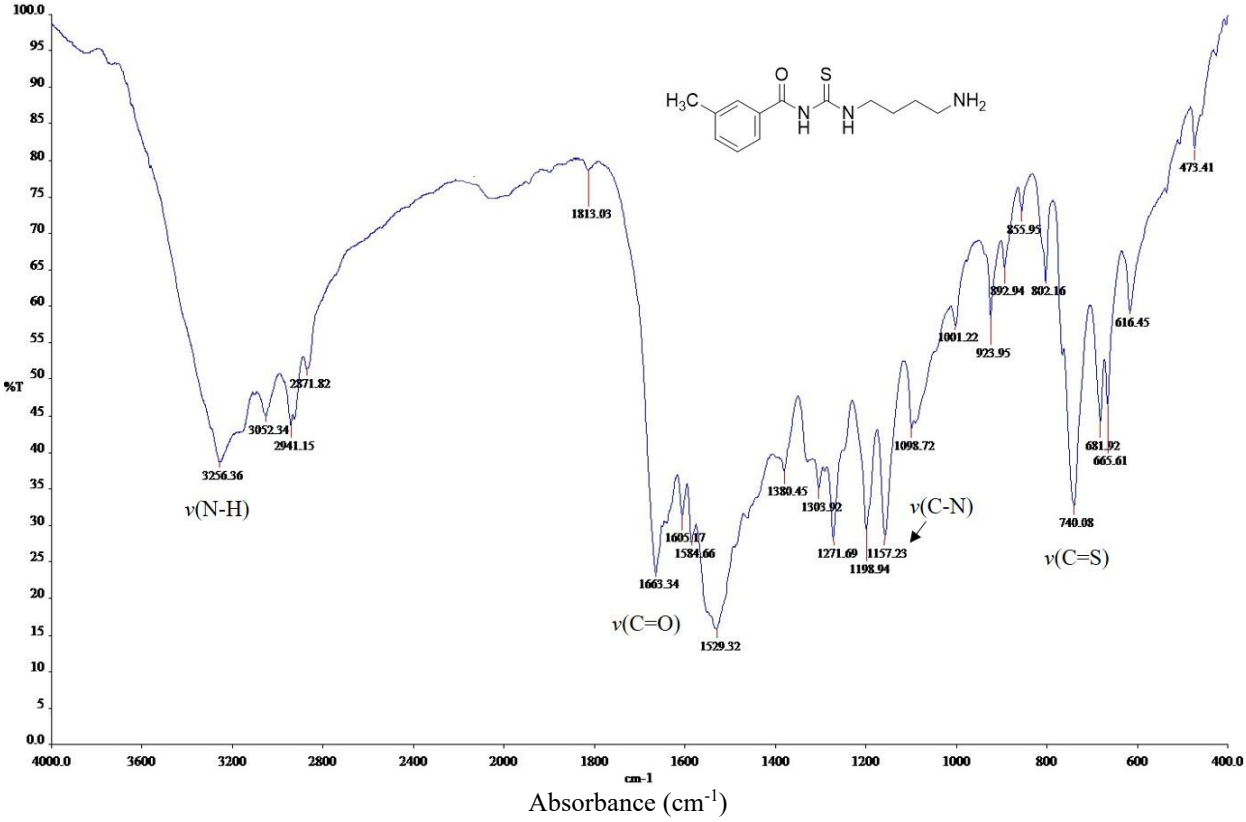


Figure 2. FTIR spectrum of **3-MBTB**

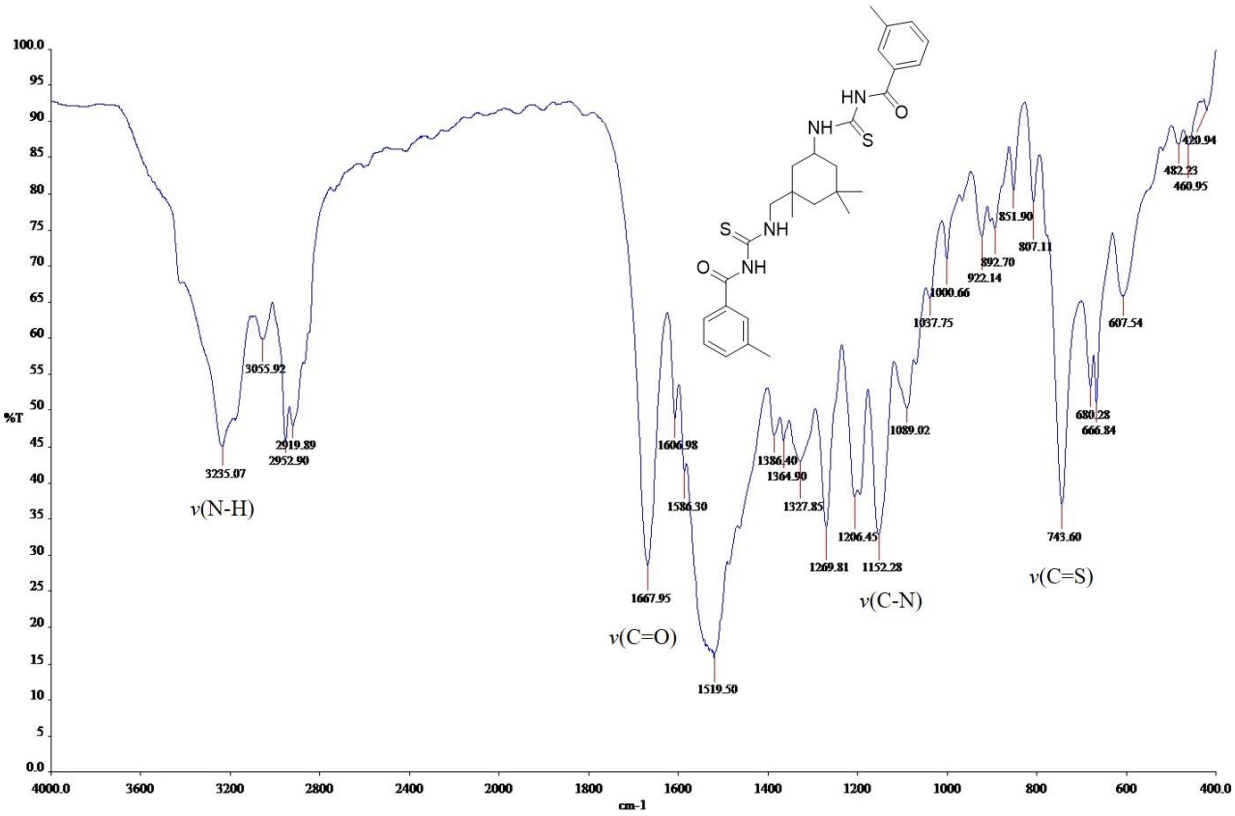


Figure 3. FTIR spectrum of **3-MBTC**

Table 1. Chemical shifts of ^{1}H and ^{13}C-NMR of 3-MBTB and 3-MBTC

		Moieties	**Chemical shifts δ_H, (ppm)**
^{1}H-NMR	3-MBTB	(m, 4H, 2×CH_2)	1.47–1.70
		(s, 3H, CH_3)	2.37
		(m, 4H, 2×CH_2)	3.62–3.68
		(m, 4H, C_6H_4)	7.37–7.76
		(m, 1H, NH)	10.91
	3-MBTC	(s, 1H, NH)	11.19
		(m, 18H, $C_{10}H_{18}$)	0.94–1.26
		(s, 6H, 2×CH_3)	2.35, 2.37
		(m, 8H, 2×C_6H_4)	7.37–7.80
		(m, 1H, NH)	10.83
		(m, 1H, NH)	11.19
		(s, 1H, NH)	11.27
		(s, 1H, NH)	11.30
^{13}C-NMR	3-MBTB	(CH_2)	21.0, 25.2, 26.6, 44.5
		(CH_3)	20.9
		(CH ar)	127.1–131.7
		(C=O)	166.3
	3-MBTC	(C=S)	180.0
		(2×CH_3)	20.8, 23.1
		($C_{10}H_{18}$)	26.7–48.3
		(2×CH ar)	125.7–137.8
		(2×C=O)	168.4, 168.6
		(2×C=S)	179.0, 180.9

NMR Spectroscopy

In the proton NMR spectra, the most upfield and shielded region belonged to aliphatic protons that can be observed in the range of δ_H 1.47-1.70 ppm (**3-MBTB**) and δ_H 0.93-1.26 ppm (**3-MBTC**). Singlet proton resonances were observed in the range of δ_H 2.35-2.37 ppm, which were attributed to the methyl moieties at the phenyl ring. In 3-MBTB, the aliphatic protons bonded to the amino group were detected in the range of δ_H 3.62–3.68 ppm due to the inductive effect of nitrogen atom that increased the chemical shift of the protons. Unresolved resonance for aromatic protons was observed in the range of δ_H 7.37-7.80 ppm due to the overlapping between proton signals in the aromatic rings [13]. Resonance for C=S-NH proton appeared in the range of δ_H 10.91-11.19 ppm, while C=O-NH proton was detected in the range of δ_H 11.19-11.30 ppm. Both of these resonances were observed at the most deshielded region in the spectra due to the electron-withdrawing moieties which then decreased the electron density around the resonances and shifted to the downfield region. Figure 4 shows ^{1}H-NMR spectrum of 3-MBTB and Figure 5 shows ^{13}C-NMR spectrum of 3-MBTC.

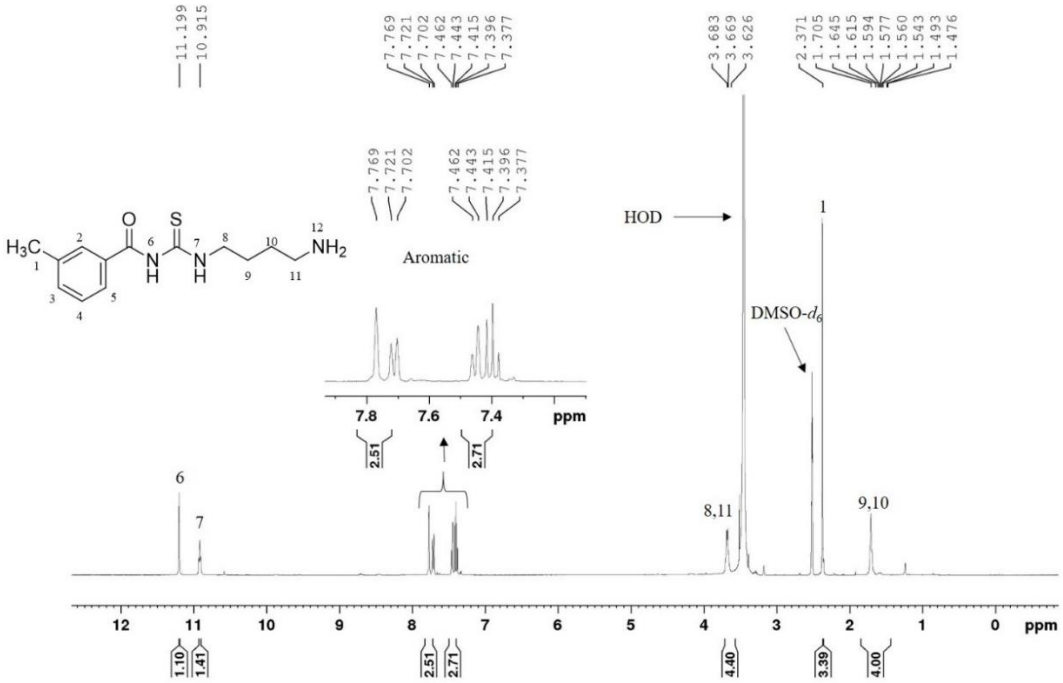


Figure 4. ^{1}H-NMR spectrum of 3-MBTB

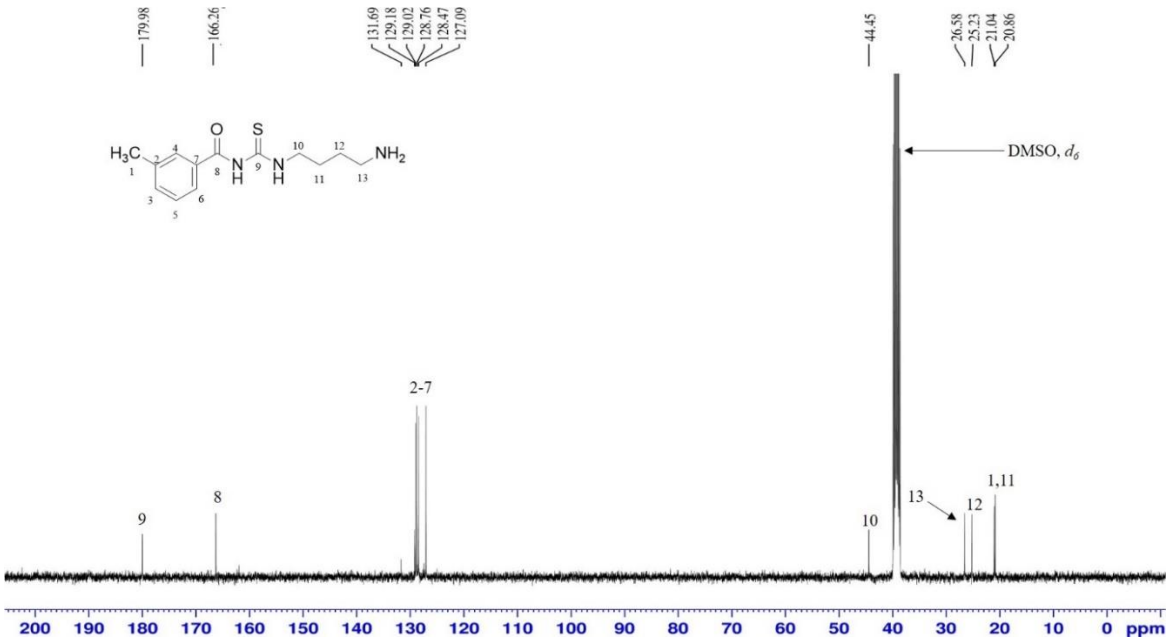


Figure 5. ^{13}C-NMR spectrum of 3-MBTC

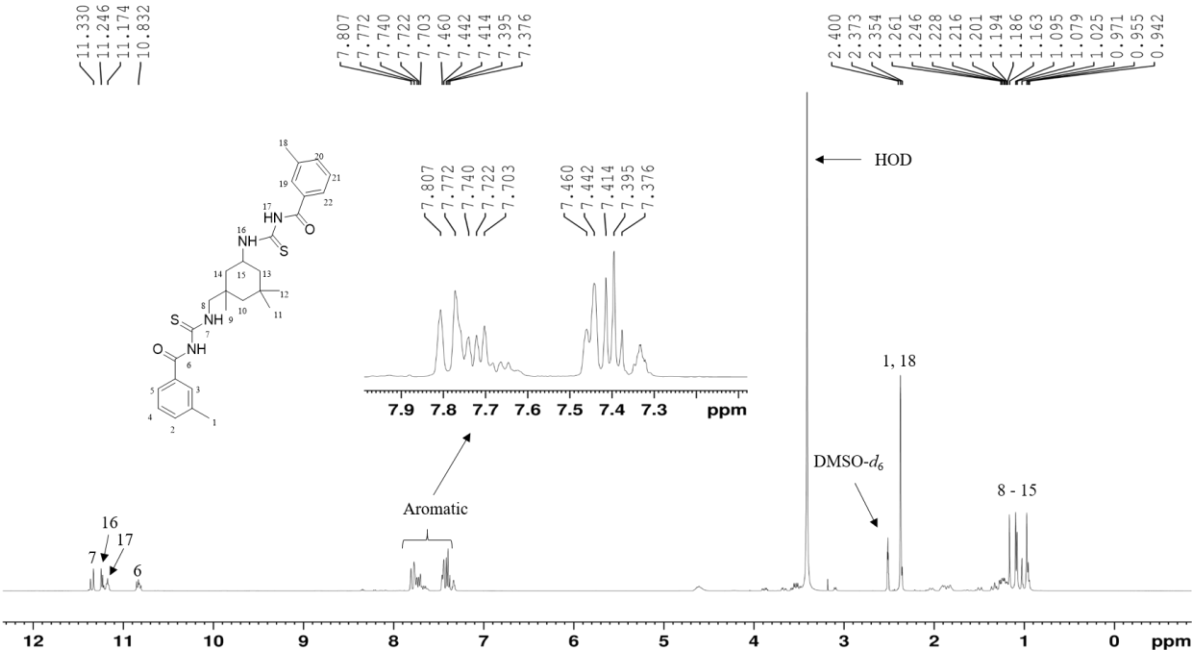


Figure 6. ^{1}H-NMR spectrum of 3-MBTC

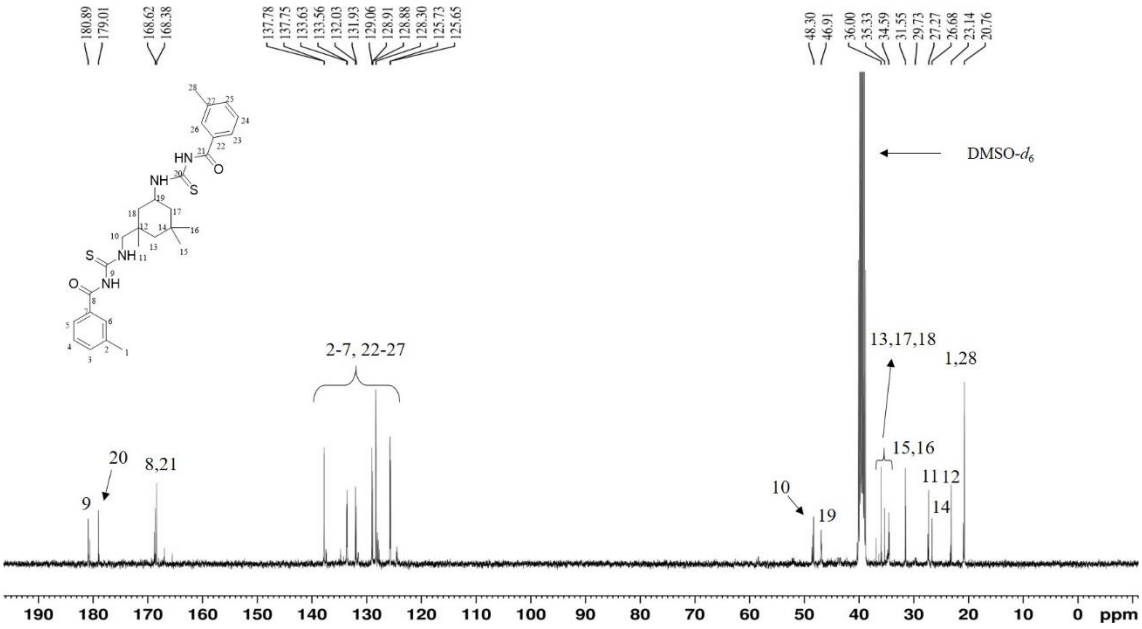


Figure 7. ^{13}C-NMR spectrum of 3-MBTC

Meanwhile, carbon NMR spectra of 3-MBTB and 3-MBTC showed the upfield and shielded region in the range of δ_C 20.8-23.1 ppm that belonged to methyl moieties. Carbon resonance of the alkyl group was detected in the range of δ_C 21.0-48.3 ppm. While the signal for aromatic ring carbon appeared in the range of δ_C 125.7-137.8 ppm. Two distinctive resonances could be observed in the most deshielded region which corresponded to carbonyl (C=O) and (C=S). Carbon resonance for C=O could be observed in the range of δ_C 166.3-168.6 ppm while carbon resonance for C=S could be observed in the range of δ_C 179.01-180.89 ppm. Table 1 shows the chemical shifts of ^{1}H and ^{13}C-NMR of 3-MBTB and 3-MBTC. Figure 4 shows ^{13}C-NMR spectrum of 3-MBTB and Figure 5 shows ^{13}C-NMR spectrum of 3-MBTC.

CHNS Elemental Analysis

The CHNS elemental analysis showed good agreements with the theory (Table 2), but with slight differences of the data obtained and the theory that might be due to traces of the solvent.

Table 2. CHNS elemental analysis for **3-MBTC** and **3-MBTB**

		Percentage of element			
		%C	%H	%N	%S
3-MBTC	Theoretical	*58.84*	*7.22*	*15.83*	*12.08*
	Experiment	58.94	6.87	14.50	11.85
3-MBTB	Theoretical	*64.09*	*6.91*	*10.68*	*12.22*
	Experiment	60.90	6.47	10.48	11.47

Mass Spectroscopy

From the spectra of **3-MBTB** (Figure 8) and **3-MBTC** (Figure 9), the molecular ions $[M]^+$ recorded for the samples were in agreement with the theoretical values. **3-MBTB** and **3-MBTC** showed the molecular ions $[M]^+$ in weak intensity at *m/z* 265 amu and *m/z* 524 amu, respectively. The base peak for both series appeared at *m/z* 119 that was assigned as cleavaged fragment of methyl benzoyl. Both of the series were detected in weak intensity probably due to unsuitable temperature and pressure used for the samples that caused the molecular ions to be unstable [15]. Based on this finding, both of the samples were indicated to be successfully obtained.

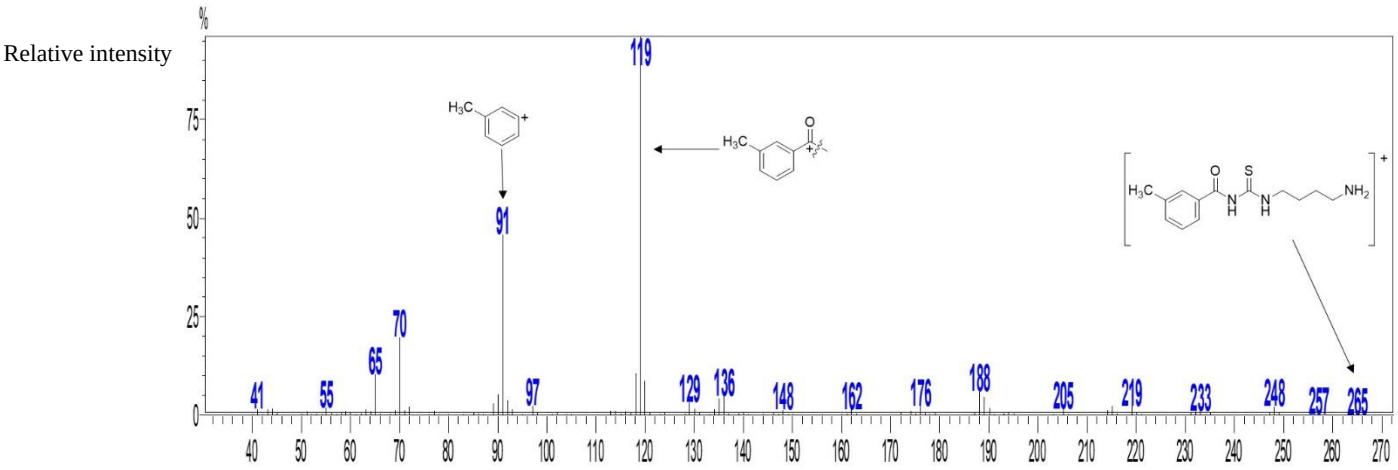


Figure 8. Mass spectrum of **3-MBTB**

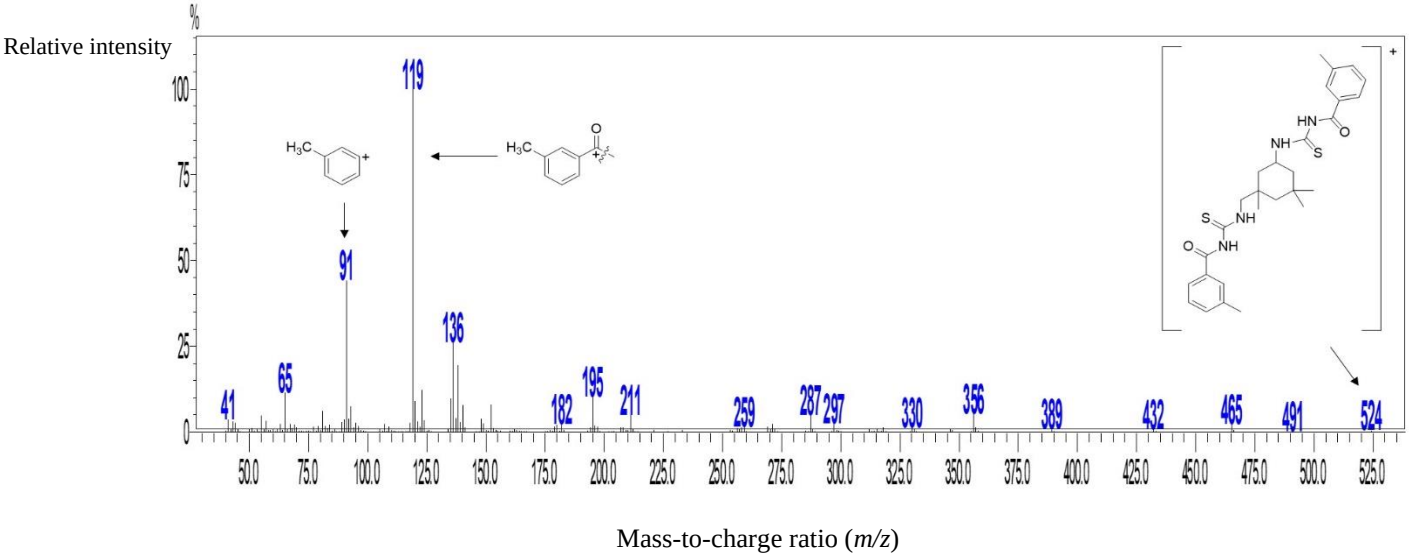
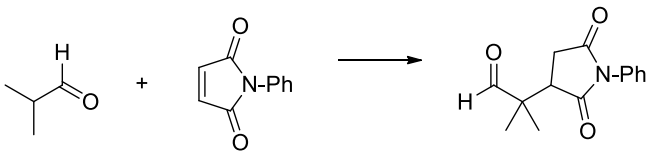


Figure 9. Mass spectrum of **3-MBTC**



Isobutyraldehyde *N*-Phenylmalemide 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal

Scheme 1. General scheme for Michael addition reaction of *N*-phenylmaleimide and Isobutyraldehyde.

Catalytic Study

The catalytic activity of 3-MBTB and 3-MBTC was evaluated in Michael addition reaction of *N*-phenymaleimide with isobutyraldehyde. Scheme 1 shows the general scheme for the Michael addition reaction. The catalytic activity of 3-MBTB and 3-MBTC was optimized using three parameters to increase the efficiency of catalytic performance .which were solvent, catalyst loading, and reaction time.

The performance of a catalysts is strongly influenced by the solvent used in the catalytic process. A solvent consists of four properties that could affect the catalytic reaction, which are solubility of the reagent, solvent interaction with the starting materials or products, solvent interaction with the catalyst, and transition state stabilization. The effects of different solvents were observed using dichloromethane, toluene, and methanol. The reactions were carried out for 6 h at room temperature with 20 mol% catalyst loading. The percentage conversion obtained is summarized in Table 3.

Based on Table 3, dichloromethane showed the highest conversion with 68% and 59% of conversion for 3-MBDB and 3-MBTC, respectively. Both dichloromethane and toluene were non-polar solvents which could help to stabilize the highly reactive catalytic intermediate. Toluene has a lower conversion compare to dichloromethane due to the lower of dielectric constant, where dielectric constant for toluene was 2.38, while dichloromethane was 9.10. The efficiency of the solvent will increase when the dielectric constant is higher because it can cause more ionization of the solute that results in more solubilisation of the sample [16]. Meanwhile, methanol showed the lowest conversion due to the formation of hydrogen bonds between the substrates and solvent [2]. As a result, dichloromethane was selected as the suitable solvent in this reaction.

The reaction condition was further optimized for catalyst loading. The amount of catalyst present in the system could affect the efficiency of the catalytic activity [17]. The results obtained are summarized in Table 3. To study the influence of catalyst loading on the conversion of *N*-phenylmalemide, three different catalyst loadings of 10, 20, and 30 mol% were selected. The results obtained are summarized in Table 4.

Table 3. Effects of solvents on Michael addition reaction of *N*-phenylmaleimide and isobutyralehyde

Entry	Solvent	Conversion of *N*-phenylmaleimide (%)	
		3-MBDB	3-MBTC
1	Dichloromethane	68	59
2	Toluene	50	45
3	Methanol	15	12

Reaction condition: [*N*-phenylmaleimide] = 0.20 mmol; [isobutyraldehyde] = 0.40 mmol; catalyst loading = 20 mol%; solvent = 1 mL

Table 4. Effects of catalyst loading in Michael addition reaction of *N*-phenylmalemide and isobutyraldehyde

Entry	Catalyst Loading (mol%)	Conversion of *N*-phenylmaleimide (%)	
		3-MBDB	3-MBTC
1	10	49	45
2	20	68	59
3	30	69	61

Reaction condition: [*N*-phenylmaleimide] = 0.20 mmol; [isobutyraldehyde] = 0.40 mmol; DCM = 1 mL; room temperature; time = 6 h

Table 5. Effects of reaction time on Michael addition reaction of *N*-phenylmaleimide.

Entry	Time (hours)	Conversion of *N*-phenylmaleimide (%)	
		3-MBDB	3-MBTC
1	6	68	59
2	12	73	61
3	24	76	72
4	48	76	72
5	72	76	72

Reaction condition: [*N*-phenylmaleimide] = 0.20 mmol; [isobutyraldehyde] = 0.40 mmol; catalyst loading = 20 mol%; DCM = 1 mL; room temperature

As shown in Table 4, a higher significant conversion of *N*-phenylmaleimide was observed at 20 mol% of catalyst loading with 68% and 59% of conversion for 3-MBDB and 3-MBTC, respectively. The conversion of *N*-phenylmaleimide was increased with 10 mol% to 20 mol% increase of catalyst loading. While with further increase of catalyst loading, no significant increase in conversion was observed. This was due to the catalyst saturation at 20 mol% and further addition of catalyst caused a negligible effect. Thus, 20 mol% of catalyst loading was chosen to test the next parameter.

The reaction was carried out at different time intervals, which were 6, 12, 24, 48, and 72 hours in order to study the reaction time. The results obtained are summarized in Table 5.

Based on Table 5, the conversion of *N*-phenylmaleimide was only active up to 24 h with 76% and 72% of conversion for 3-MBDB and 3-MBTC, respectively. After 24 h, the conversion was constant for both catalysts due to the saturation between the catalyst and reactant. The conversion was almost constant after a certain time due to the reaction equilibrium was achieved between the catalyst and reactant [18]. Therefore, in this reaction, 24 h reaction time was the suitable condition for the use of 3-MBDB and 3-MBTC as organocatalysts.

In this study, the highest conversion was only achieved up to 76% (3-MBDB) and 72% (3-MBTC), while the conversion from a previous study reached up to 90%. Lower conversions were obtained in this study because the organocatalysts used were less acidic compared to previously reported. Besides, the compound reported in the study as an organocatalyst consisted of trifluoromethyl, which is more acidic compared to carbonyl. Acidic additives play an important role in improving a conversion by accelerating the formation of enamine intermediates [19]. In this study, 3-MBDB had a better catalytic activity compared to 3-MBTC due to the steric effect of the compound.

CONCLUSIONS

In conclusion, two new methylbenzoylthiourea derivatives were successful synthesized and characterized using FTIR, NMR, CHNS elemental analysis, and mass spectrometry. Besides, the catalytic performance for the synthesized compounds showed good yields, which were up to 72% and 76%. Both of the synthesized compounds showed good potentials as organocatalysts.

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REFERENCES

1. Pohlmann, J., Lampe, T., Shimada, M., Nell, P. G., Pernerstorfer, J., Svenstrup, N., Brunner, N. A., Schiffer, G. & Freiberg, C. (2005) Pyrrolidinedione derivatives as antibacterial agents with a novel mode of action. *Bioorganic & Medicinal Chemistry Letters*, **15(4)**, 1189–1192.

2. Ma, Z. W., Liu, Y. X., Li, P. L., Ren, H., Zhu, Y. & Tao, J. C.(2011) A highly efficient large-scale asymmetric Michael addition of isobutyraldehyde to maleimides promoted by a novel multifunctional thiourea. *Tetrahedron: Asymmetry*, **22(18)**, 1740–1748.

3. Cao, Y. J., Lai, Y. Y., Wang, X., Li, Y. J. & Xiao, W. J. (2007) Michael additions in water of ketones to nitroolefins catalyzed by readily tunable and bifunctional pyrrolidine–thiourea organocatalysts. *Tetrahedron Letters*, **48(1)**, 21–24.

4. Miyabe, H. (2016) Hydrogen-Bonding Activation in Chiral Organocatalysts. *Recent Advances in Organocatalysis*, **1**.

5. Bai, J. F., Peng, L., Wang, L. l., Wang, L. X. & Xu, X. Y. (2010) Chiral primary amine thiourea promoted highly enantioselective Michael reactions of isobutylaldehyde with maleimides. *Tetrahedron*, **66(46)**, 8928–8932.

6. Durmaz, M. & Sirit, A. (2013) Calixarene-based chiral primary amine thiourea promoted highly enantioselective asymmetric Michael reactions of α, α-disubstituted aldehydes with maleimides. *Tetrahedron: Asymmetry*, **24(23)**, 1443–1448.

7. Avila-Ortiz, C. G., Díaz-Corona, L., Jiménez-González, E. & Juaristi, E. (2017) Asymmetric Michael addition organocatalyzed by α, β-dipeptides under solvent-free reaction conditions. *Molecules*, **22(8)**, 1328.

8. Nakashima, K., Kawada, M., Hirashima, S. I., Kosugi, A., Kato, M., Yoshida, A. & Miura, T. (2016) Stereoselective conjugate addition of carbonyl compounds to maleimides using a diaminomethyleneindenedione organo-catalyst. *Tetrahedron: Asymmetry*, **27(17)**, 888–895.

9. Uddin, J., Ueda, K., Siwu, E. R., Kita, M. & Uemura, D. (2006) Cytotoxic labdane alkaloids from an ascidian Lissoclinum sp.: isolation, structure elucidation, and structure–activity relationship. *Bioorganic & medicinal chemistry*, **14(20)**, 6954–6961.

10. Córdova, A., Xu, Y., Sundén, H., Eriksson, L., Sayah, M. & Zhao, G. L. (2007) Organocatalytic enantioselective conjugate addition of aldehydes to maleimides. *Chemical Communications*, **7**, 734–735.

11. Xue, F., Liu, L., Zhang, S., Duan, W., & Wang, W. (2010) A Simple Primary Amine Thiourea Catalyzed Highly Enantioselective Conjugate Addition of α, α-Disubstituted Aldehydes to Maleimides. *Chemistry-A European Journal*, **16(27)**, 7979–7982.

12. Kumari, R. G., Ramakrishnan, V., Carolin, M. L., Kumar, J., Sarua, A. & Kuball, M. (2009) Raman spectral investigation of thiourea complexes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectro-scopy*, **73(2)**, 263–267.

13. Yusof, M. S. M., Khairul, W. M., & Yamin, B. M. (2010) Synthesis and characterisation a series of N-(3, 4-dichlorophenyl)-N′-(2, 3 and 4-methylbenzoyl) thiourea derivatives. *Journal of Molecular Structure,* **975(1)**, 280–284.

14. Khairul, W. M., Zuki, H. M., Hasan, M. F. A., & Daud, A. I. (2016) Pyridine Acyl Thiourea as Ionophore for the Detection of Copper (II) in Aqueous Phase. *Procedia Chemistry*, **20**, 105–114.

15. Skoog, D. A., Holler, F. J. & Crouch, S. R. (2007) *Principles of instrumental analysis*. Cengage learning.

16. Fakhree, M. A. A., Delgado, D. R., Martínez, F. & Jouyban, A. (2010) The importance of dielectric constant for drug solubility prediction in binary solvent mixtures: electrolytes and zwitterions in water+ ethanol. *Aaps Pharmscitech*, **11(4)**, 1726–1729.

17. Radwan, N. R., Hagar, M., Afifi, T. H., Al-wadaani, F. & Okasha, R. M. (2018) Catalytic Activity of Sulfated and Phosphated Catalysts towards the Synthesis of Substituted Coumarin. *Catalysts*, **8(1)**, 36.

18. Wei, T., Wang, M., Wei, W., Sun, Y. & Zhong, B. (2003) Synthesis of Dimethyl Carbonate from Propylene Carbonate and Methanol over Mesoporous Solid Base Catalyst. *Chemical Industries-New York-Marcel Dekker*, 659–666.

19. Yu, F., Jin, Z., Huang, H., Ye, T., Liang, X., & Ye, J. (2010) A highly efficient asymmetric Michael addition of α, α-disubstituted aldehydes to maleimides catalyzed by primary amine thiourea salt. *Organic & biomolecular chemistry*, **8(20)**, 4767–4774.