

Metal-free approach for one-pot synthesis of 3-aryl-furo[3,2-c]coumarins

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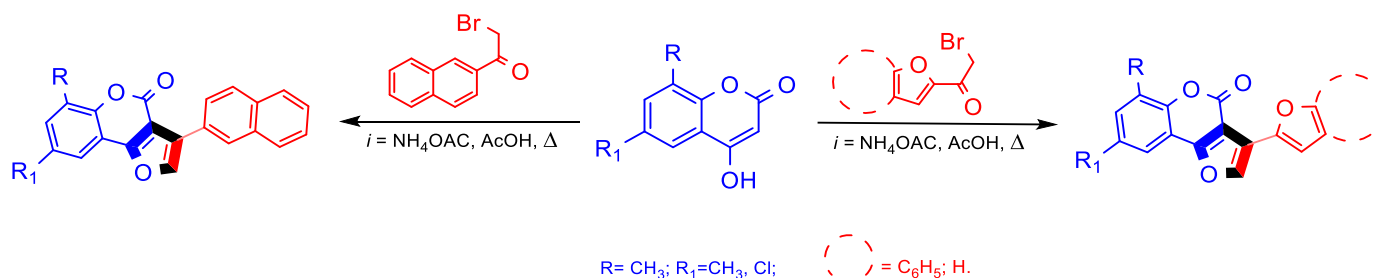
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Abstract

Various 3-aryl-furo[3,2-c]coumarins have been synthesized by reacting various 4-hydroxycoumarins with appropriate bromo-acetyl derivatives of furan, naphthalene and benzofuran under metal-free reaction condition. The effects of substitution, reaction temperature and reaction time for product formation were investigated. All the synthesized compounds were characterized by IR, ¹H NMR, ¹³C NMR, DEPT-90, Mass spectral and elemental analysis.



Keywords: Furo[3,2-c]coumarin, naphthalene, furan, benzofuran, metal-free reaction condition

Introduction

Coumarins are important members of naturally occurring oxygen-containing heterocyclic compounds. Coumarins are produced by certain bacteria, fungi and numerous plant species like Umbelliferae, Asteraceae, Rutaceae, and Leguminoase,^{1,2} nearly 1300 coumarin derivatives are identified as secondary metabolites from the same sources. Coumarins belong to the family of benzopyrones which are a fusion of pyrone with a benzene ring. They contain an electronically rich conjugated system which exerts good charge transport properties so numerous reactions possible on them. Coumarins showed cytotoxic activity against numerous types of cancers³ and certain types of activities like anti-microbial,⁴ antioxidant,⁵ antiviral,⁶ anti-tuberculosis,⁷ are also reported. Coumarins found use in optical applications, solar energy collectors, as luminescent materials,⁸ in cosmetics and food additives.⁹ Due to its capacious range of applications, coumarins become significant synthetic target materials.

In recent times, chemists put their efforts to increase the complexity of structures¹⁰ and in the same instance, they wanted to decrease the number of reaction steps to obtain the desired products. Heterocyclic fused coumarin derivatives attract researchers due to its wide range of biological properties. Numerous heterocyclic ring fusion on lactone ring of coumarin have been reported such as pyrido,¹¹ pyrano,¹² pyrrole,¹³ furan,¹⁴ thiophene,¹⁵ indole,¹⁶ oxazole,¹⁷ thiazole.¹⁸ But amongst them all, a fusion of furan with coumarin termed as furocoumarin is a prominent class of tricyclic aromatic compounds. Furocoumarins and their analogs are widely unrolled in nature and found in numerous plant species such as Umbelliferae and Rutaceae.¹⁹ They are also naturally occurring as a psoralene and angelicine and are used in the treatment of skin diseases.²⁰ Many furocoumarin derivatives exert impressive biological and pharmacological properties (Figure 1) like anticoagulant,²¹ antibacterial,²² antifungal,²³ anti-inflammatory.²⁴ Several furocoumarins are reported to inhibit the growth of cancer cells.^{25,26}

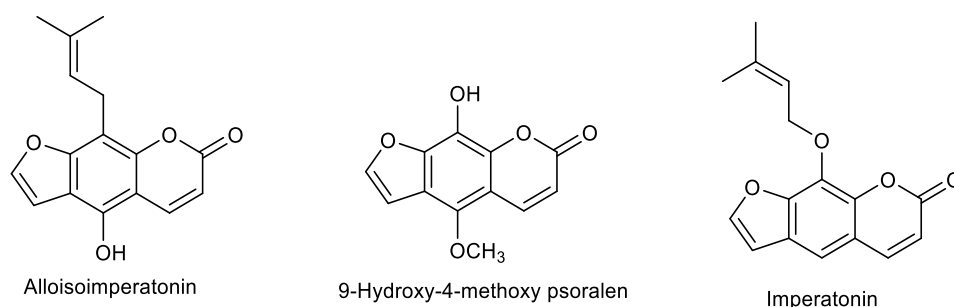


Figure 1. Reported potent furocoumarins.

Furocoumarins have predominantly three different structural isomers: furo[3,2-*c*]coumarin, furo[3,4-*c*]coumarin and furo[2,3-*c*]coumarin. Amongst all oxygen-containing heterocyclic fused coumarins, furo[3,2-*c*]coumarins are significantly important for medicinal purposes and eye attracting for organic chemistry. furo[3,2-*c*]coumarin derivatives have a wide range of biological and pharmacological activities.^{27,28} Naturally occurring furo coumarins like psoralens and angelicin are used to treat vitiligo,^{29,30} psoriasis,³¹ and cancer.³² Because of such important applications of furo[3,2-*c*] coumarin, several distinct protocols have been revealed to achieve these scaffolds in recent times. Among others, synthesis carried out using sodium hydride,³³ trimethylchlorosilane, rhodium, palladium like metal catalysts are influential because they allow the construction of complex furocoumarins.³⁴ Tetraphenyl-porphyrin like synthetic porphyrin³⁵ used as catalysts

for the synthesis of furo[3,2-*c*]coumarins. Several researchers reported the applications of white LEDs as visible light energy source³⁶ for the synthesis of furo[3,2-*c*]coumarin derivatives.

On the other hand, molecules like furan, benzofuran, and naphthalene are resourceful building blocks for an organic synthetic chemist due to their structural diversity as well as biological potencies.^{37-41,42}

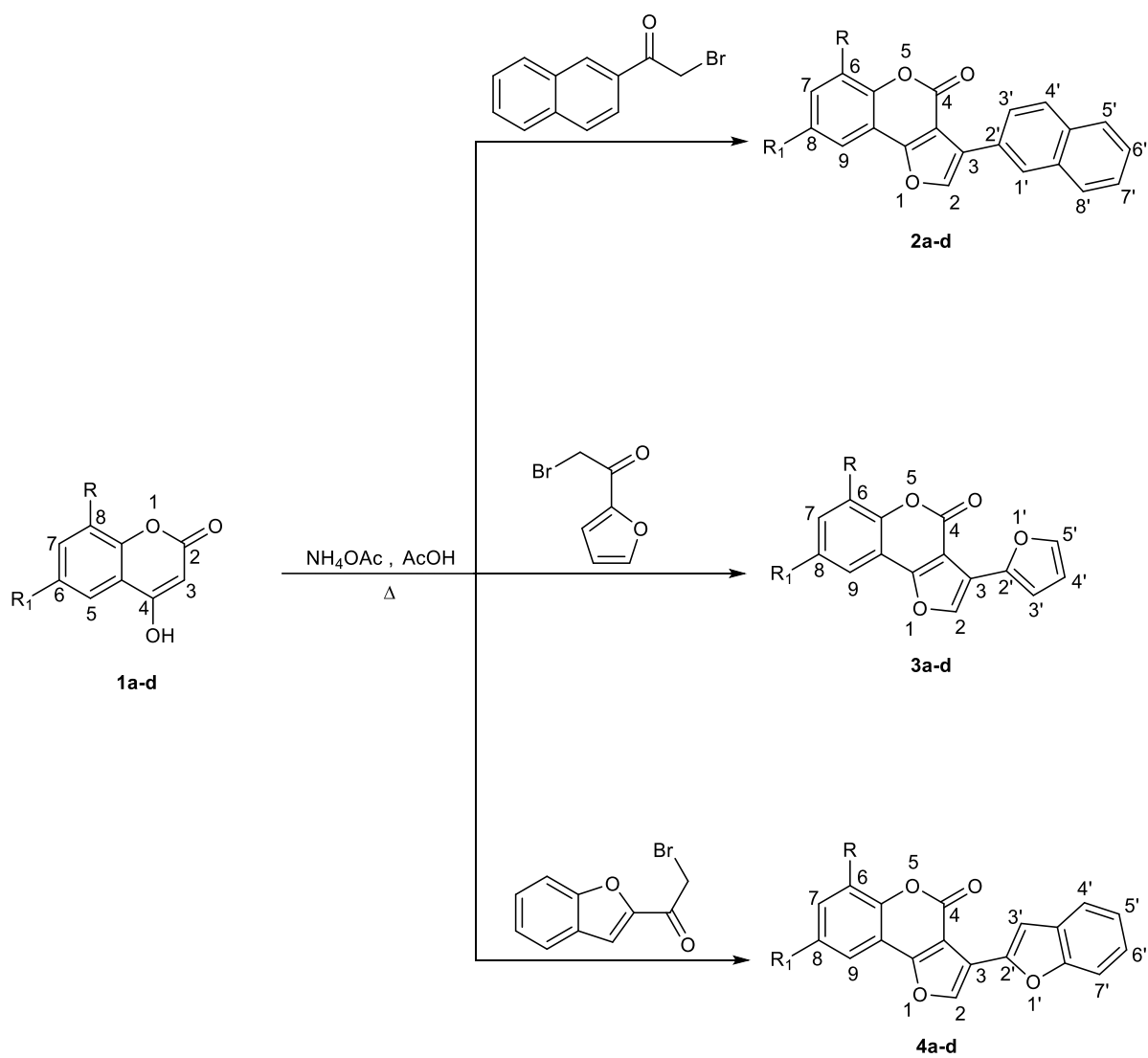
Hence, in order to acquire a complex heterocyclic system having a minimum of two components such as coumarin with biologically active compounds like furan, benzofuran or naphthalene, a one-pot synthesis strategy is carried out. A one-pot synthesis is a powerful strategy to incorporate many pharmacophores in one molecule. This strategy is used in organic chemistry to enhance the efficiency in the congregation of novel fused-ring entities. This approach allows multifold reaction steps to be carried out in a single reaction vessel by multiple bond-forming events in one operation and reduces lengthy workup processes that save time as well as resources. Generally, for the synthesis of complex heterocyclic molecules, metal-catalyzed reaction conditions used for easy operations but the consumption of such metal exerts harmful effects on environment.⁴³ The metals used for reactions are heavy metals such as zinc, copper, cobalt, titanium, cadmium, arsenic, mercury, and lead are responsible for water and soil pollution which will indirectly affect the quality of our food. So, it essential to use metal-free reaction conditions for the conservation of our natural resources and metal-free environment.

Considering the significant importance of furo[3,2-*c*]coumarins, our ongoing interest in building up coumarin-based heterocyclic compounds⁴⁴ prompted us to dedicate our efforts to design and synthesis a series of novel furo[3,2-*c*]coumarin derivatives via one-pot approach using metal-free reaction conditions.^{45,46} From the synthesis point of view, these compounds open-up huge possibilities for a broad range of bounteous complex heterocycles due to more exposure to its pharmacophores.

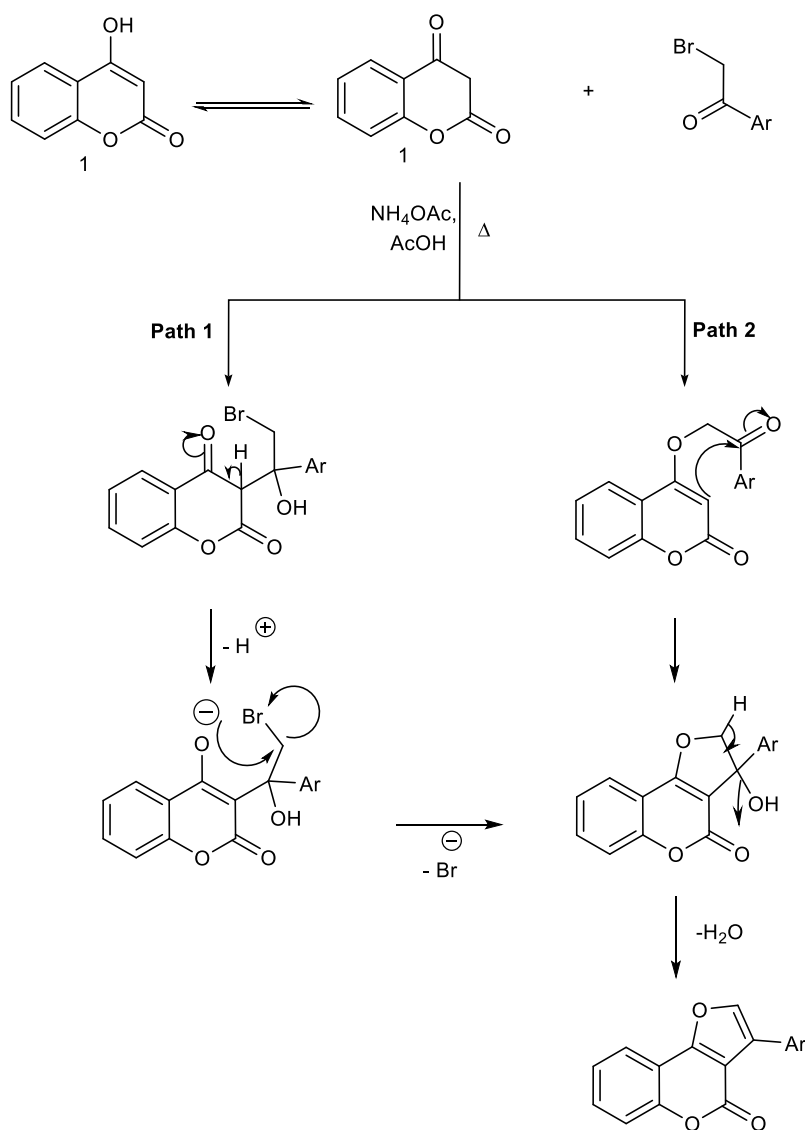
Results and Discussion

In order to synthesize 3-aryl-Furo[3,2-*c*]coumarins **2a-d**, **3a-d** and **4a-d**, various 4-hydroxy coumarin derivative **1a-d** reacted with appropriate bromo acetyl derivatives such as 2-bromo-acetyl naphthalene, 2-bromo-acetyl furan, 2-bromo-acetyl benzofuran respectively in the presence of ammonium acetate in refluxing acetic acid to afford 3-(naphthalene-2-yl)-4*H*-furo[3,2-*c*]chromen-4-one (**2a-d**), 3-(furan-2-yl)-4*H*-furo[3,2-*c*]chromen-4-one (**3a-d**), 3-(benzofuran-2-yl)-4*H*-furo[3,2-*c*]chromen-4-one (**4a-d**) respectively [Scheme 1]. The reaction pathway is assumed to proceed by Michael addition of the active methylene function of 4-hydroxy coumarin on bromo-acetyl derivatives, resulting in the formation of **2a-d**, **3a-d** and **4a-d**. The proposed mechanism is shown in Scheme 2.

The reaction conditions were obtained for the optimum reaction. The study of percentage yield, reaction temperature and reaction time for the synthesized compounds are varied due to the presence of different substitution over furo[3,2-*c*]coumarin derivatives [Table 1]. Data shows that the presence of electron-donating groups on the 8th position of furo[3,2-*c*]coumarin derivatives mostly favours the smooth reaction progression with shorter reaction completion time and higher percentage yield. Similarly, in presence of electron-donating group on 6th position of furo[3,2-*c*]coumarin derivatives moderately favours the reaction but however, presence of electron-withdrawing group on the 8th position of furo[3,2-*c*]coumarin derivatives little bit obstructs the reaction progression that results into consumption of longer duration of time for completion of reaction and low percentage of yield was observed. Furthermore, reaction temperature plays an important role in the transformation of final products. It was observed that raise in reaction temperature from 140 °C to 160 °C can remarkably influence product formation in terms of reaction time [Table 2].



Scheme 1. 3-Aryl-furo[3,2-c]coumarins.



Scheme 2. Possible mechanism of 3-aryl-furo[3,2-c]coumarin derivatives.

Table 1. 4-Hydroxy coumarin derivatives

Compound	R_1	R
1a	H	H
1b	H	CH_3
1c	CH_3	H
1d	Cl	H

Table 2. Furo[3,2-c]coumarin derivatives (**2a-d**, **3a-d** and **4a-d**)

Compound	R	R ¹	At 140 °C		At 160 °C	
			Reaction Time(min)	% Yield	Reaction Time(min)	% Yield
2a	H	H	240	71	190	70
2b	CH ₃	H	210	75	170	74
2c	H	CH ₃	200	74	170	72
2d	H	Cl	250	65	200	65
3a	H	H	240	64	180	62
3b	CH ₃	H	220	68	180	65
3c	H	CH ₃	150	66	130	64
3d	H	Cl	240	56	190	55
4a	H	H	180	65	130	65
4b	CH ₃	H	160	70	120	68
4c	H	CH ₃	120	68	90	66
4d	H	Cl	200	61	150	61

The structures of all the synthesized compounds were established on the basis of FT-IR, ¹H-NMR, ¹³C-NMR, and DEPT-90 spectral data. Mass spectroscopic data provided the molecular weights. Elemental analysis of the molecules confirmed their molecular formula.

The IR spectra of **2a-d**, **3a-d** and **4a-d** exhibited characteristic bands between 1724-1751 cm⁻¹ for carbonyl stretching vibrations of the δ -lactone carbonyl (C=O) stretching, bands between 1615-1650 cm⁻¹ for aromatic C=C stretching and bands between 2922-3160 cm⁻¹ for C-H stretching vibrations respectively.

The NMR spectrum of compounds **2a-d** showed various spin multiplicities between 7.38-8.13 δ ppm for aromatic protons, a characteristic singlet observed between 8.50-8.64 δ ppm. The C₉-H appeared as singlet for compound **2c** & **2d** due to the absence of neighbouring proton and doublet observed for compound **2a** & **2b** due to the presence of one neighbouring proton. C₉-H appeared more downfield region between 8.25-8.45 δ ppm due to the peri effect of the oxygen atom of fused furan ring. The NMR spectrum of compounds **3a-d** showed various spin multiplicities between 7.30-8.16 δ ppm for aromatic protons, a characteristic singlet observed between 8.28-8.52 δ ppm. The NMR spectrum of compounds **4a-d** showed various spin multiplicities between 7.22-7.77 δ ppm for aromatic protons, a characteristic singlet observed between 8.23-8.83 δ ppm. The C_{2'}-H appeared as singlet between 7.90-8.07 δ ppm. The C₉-H appeared as singlet for compound **4c** & **4d** due to the absence of neighbour proton and doublet observed for compound **4a** & **4b** due to the presence of one neighbour proton. C₉-H appeared more downfield region between 7.79-7.93 δ ppm due to the peri effect of the oxygen atom of fused furan ring. The C_{2'}-H appeared as singlet between 7.90-8.07 δ ppm.

The ¹³C-NMR spectra of compounds **2a-d**, **3a-d** and **4a-d** showed signals for carbonyl carbon in a δ -lactone ring around 160.0 δ ppm. The aromatic carbons appeared between δ ppm 105.0 and 155. Mass spectra of compound **2a** gave molecular ion peak at 312.0 [M+H]⁺ corresponding to molecular formula C₂₁H₁₂O₃. All other compounds gave satisfactory spectral data which are given in the experimental section.

Conclusions

This investigation represents a straightforward and efficient metal-free route that has been developed for the synthesis of 3-aryl-furo[3,2-c]coumarins analogues. We perceive the presence of various substitution over coumarins affects reaction feasibility, the substitution of electron-donating group enhances the feasibility of overall reaction and yield, whereas the presence of electron-withdrawing group on coumarins limits the feasibility of reaction for the synthesis of 3-aryl-furo[3,2-c]coumarins analogues. In addition, the impact of elevated temperature favours the completion of the reaction in less time. Furo[3,2-c]coumarins skeleton with associated pharmacophores increases the structural diversity of final products. We expect that the resulting compounds are endowed with active functions are expected to contribute a broader range of biological applications.

Experimental Section

General. Reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined by the μ ThermoCal10 melting point apparatus. Thin-layer chromatography (TLC, Aluminium plates coated with silica gel 60 F254, 0.25 mm thickness, Merck) were used for monitoring the progress of all reactions, purity, and homogeneity of the synthesized compounds. FT-IR spectra were recorded using potassium bromide disc on Nicolet 6700 FT-IR spectrophotometer and only the characteristic peaks are reported. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded using DMSO- d_6 and CDCl_3 as a solvent on a Bruker Avance spectrometer at the frequency of 400 MHz and 100 MHz respectively using TMS as an internal standard. Mass spectra were determined by Shimadzu QP2010 Spectrometer.

General procedure for the synthesis of furo[3,2-c]coumarin derivatives (2a-d, 3a-d and 4a-d). In a round bottom three-neck flask (100 mL), 4-hydroxy coumarin **1a-d** (1 mmol) was taken in glacial acetic acid (3 mL). To this solution, ammonium acetate (3 mmol) and an appropriate bromo-acetyl derivative (1 mmol) in acetic acid (2 mL) were added with stirring. The reaction mixture was stirred at room temperature for 45 minutes and then refluxed in an oil bath at 140-160°C bath temperature for 90-240 minutes. It was then poured in water (30 mL) and the crude solid obtained was extracted with chloroform (3 x 15 mL). The chloroform extract was washed with 5% NaHCO_3 , water and dried over anhydrous sodium sulfate. The removal of chloroform under vacuum resulted in gummy residue, which was subjected to column chromatography using silica-gel and ethyl acetate-pet.ether (60-80) (1:9) as an eluent to have compounds **2a-d**, **3a-d** and **4a-d** respectively [Scheme 1].

Table 3. Physical data of the synthesized compounds **2a-d**, **3a-d** and **4a-d**

Compound	Formula	Appearance	Mp(°C)	Reference
2a	$\text{C}_{21}\text{H}_{12}\text{O}_3$ ⁴⁷	White solid	202-206	47
2b	$\text{C}_{22}\text{H}_{14}\text{O}_3$	White solid	218-222	-
2c	$\text{C}_{22}\text{H}_{14}\text{O}_3$	White solid	222-226	47
2d	$\text{C}_{23}\text{H}_{14}\text{O}_3$	Off-white solid	>240	-
3a	$\text{C}_{15}\text{H}_8\text{O}_4$	Off-white solid	202-206	47

Table 3. Continued

Compound	Formula	Appearance	Mp(°C)	Reference
3b	C ₁₆ H ₁₀ O ₄	Light-blue solid	168-172	-
3c	C ₁₆ H ₁₀ O ₄	White solid	178-182	47
3d	C ₁₅ H ₇ ClO ₄	Grey solid	188-192	-
4a	C ₁₉ H ₁₀ O ₄	Off-white solid	>240	-
4b	C ₂₀ H ₁₂ O ₄	White solid	212-216	-
4c	C ₂₀ H ₁₂ O ₄	White solid	226-230	-
4d	C ₁₉ H ₉ ClO ₄	White solid	>240	-

3-(Naphthalen-2-yl)-4H-furo[3,2-c]chromen-4-one (2a). IR spectrum, ν_{\max} , cm⁻¹: 3154 & 3049 (aromatic C-H), 1738 (C=O, δ -lactone), 1626 (aromatic C=C) cm⁻¹; ¹H NMR (DMSO- *d*₆) δ , ppm (*J*, Hz): 7.50 (1H, t, *J* 8.0 Hz, Ar-H), 7.56-7.61 (3H, m, Ar-H), 7.69 (1H, ddd, *J* 15.6, 7.6 and 1.6 Hz, Ar-H), 7.92 (1H, dd, *J* 10.4 and 2.0 Hz, Ar-H), 7.96 (2H, q, *J* 4.8 Hz, Ar-H), 8.00-8.06 (2H, m, Ar-H), 8.45 (1H, d, *J* 0.8 Hz, Ar-H), 8.64 (1H, s, Ar-H); ¹³C NMR (DMSO- *d*₆) δ , ppm: 108.41(C), 112.56(C), 117.26(CH), 121.43(CH), 125.36(CH), 125.79(C), 126.90(CH), 126.95(CH), 127.05(C), 127.83(CH), 128.02(CH), 128.21(CH), 128.51(CH), 131.87(CH), 132.89(C), 133.20(C), 144.00(CH), 152.45(C), 157.61(C), 158.70(C). Anal. Calcd. for C₂₁H₁₂O₃ : C, 80.76; H, 3.87%. Found: C, 80.70; H, 3.83%. MS *m/z*: 312.0 (M⁺).

6-Methyl-3-(naphthalen-2-yl)-4H-furo[3,2-c]chromen-4-one (2b). IR spectrum, ν_{\max} , cm⁻¹: 3113 & 3050 (aromatic C-H), 1734 (C=O, δ -lactone), 1625 (aromatic C=C) cm⁻¹; ¹H NMR (DMSO- *d*₆) δ , ppm (*J*, Hz): 2.46 (3H, s, CH₃), 7.38 (1H, t, *J* 7.6 Hz, Ar-H), 7.54-7.59 (3H, m, Ar-H), 7.86 (1H, dd, *J* 7.6 and 0.9 Hz, Ar-H), 7.90 (1H, d, *J* 1.76 Hz, Ar-H), 7.93-7.97 (2H, m, Ar-H), 8.01 (1H, d, *J* 8.6 Hz, Ar-H), 8.44 (1H, s, Ar-H) 8.60 (1H, s, Ar-H); ¹³C NMR (DMSO-*d*₆) δ , ppm: 15.51(CH₃), 107.66(C), 111.79(C), 118.58(CH), 121.44(C), 124.42(CH), 125.23(C), 125.75(C), 126.42(CH), 126.48(CH), 126.61(C), 127.34(CH), 127.54(CH), 127.73(CH), 128.01(CH), 132.40(CH), 132.73(C), 143.48(CH), 150.32(C), 157.02(C), 158.59(C). Anal. Calcd. for C₂₂H₁₄O₃ : C, 80.97; H, 4.32. Found: C, 80.92; H, 4.41%. MS *m/z*: 326.0 (M⁺).

8-Methyl-3-(naphthalen-2-yl)-4H-furo[3,2-c]chromen-4-one (2c). IR spectrum, ν_{\max} , cm⁻¹: 3156 & 3049 (aromatic C-H), 1735 (C=O, δ -lactone), 1630 (aromatic C=C) cm⁻¹; ¹H NMR (DMSO- *d*₆) δ , ppm (*J*, Hz): 2.45 (3H, s, CH₃), 7.47 (2H, s, Ar-H), 7.55-7.57 (2H, m, Ar-H), 7.80 (1H, s, Ar-H), 7.89 (1H, dd, *J* 8.4 and 1.6 Hz, Ar-H), 7.93-7.99 (2H, m, Ar-H), 8.01 (1H, s, Ar-H), 8.43 (1H, s, Ar-H), 8.60 (1H, s, Ar-H); ¹³C NMR (DMSO-*d*₆) δ , ppm: 20.81(CH₃), 108.00(C), 112.12(C), 117.03(CH), 120.95(CH), 125.93(C), 126.81(CH), 126.86(CH), 126.95(CH), 127.15(C), 127.88(CH), 127.98(CH), 128.15(CH), 128.48(CH), 132.74(CH), 133.018(C), 133.33(C), 134.85(C), 143.80(CH), 150.82(C), 157.66(C), 158.79(C). Anal. Calcd. for C₂₂H₁₄O₃ : C, 80.97; H, 4.32 %. Found: C, 80.92; H, 4.41%. MS *m/z*: 326.0 (M⁺).

8-Chloro-3-(naphthalen-2-yl)-4H-furo[3,2-c]chromen-4-one (2d). IR spectrum, ν_{\max} , cm⁻¹: 3135 & 3054 (aromatic C-H), 1724 (C=O, δ -lactone), 1623 (aromatic C=C) cm⁻¹; ¹H NMR (DMSO- *d*₆) δ , ppm (*J*, Hz): 7.61 (2H, d, *J* 4.0 Hz, Ar-H), 7.67 (1H, d, *J* 8.8 Hz, Ar-H), 7.75 (1H, d, *J* 8.8 Hz, Ar-H), 7.94 (1H, d, *J* 8.4 Hz, Ar-H), 7.99-8.06 (3H, m, Ar-H), 8.11 (1H, s, Ar-H), 8.46 (1H, s, Ar-H), 8.71 (1H, s, Ar-H); ¹³C NMR (CDCl₃) δ , ppm: 109.35(C), 113.85(C), 118.67(CH), 120.58(CH), 126.13(C), 126.28(CH), 126.43(CH), 126.51(CH), 127.01(C), 127.69(CH), 127.96(CH), 128.24(CH), 128.36(CH), 130.10(C), 131.00(CH), 133.14(C), 133.31(C), 142.05(CH), 150.96(C),

157.44(C), 157.65(C). Anal. Calcd. for $C_{23}H_{14}O_3$: C, 72.74; H, 3.20%. Found: C, 72.81; H, 3.22. MS m/z : 346.0 (M^+).

3-(Furan-2-yl)-4H-furo[3,2-c]chromen-4-one (3a). IR spectrum, ν_{max} , cm^{-1} : 3143 & 2922 (aromatic C-H), 1744 (C=O, δ -lactone), 1628 (aromatic C=C) cm^{-1} ; 1H NMR (DMSO- d_6) δ , ppm (J , Hz): 6.63 (1H, dd, J 3.2 and 1.6 Hz, Ar-H), 7.37 (1H, d, J 3.6 Hz, Ar-H), 7.46 (1H, t, J 8.0 Hz, Ar-H), 7.56 (1H, d, J 7.6 Hz, Ar-H), 7.66 (1H, td J 8.4 and 1.6 Hz, Ar-H), 7.78 (1H, d, J 1.2 Hz, Ar-H), 7.97 (1H, dd, J 7.8 and 1.6 Hz, Ar-H), 8.52 (1H, s, Ar-H); ^{13}C NMR (DMSO- d_6) δ , ppm: 106.70(C), 111.40(CH), 112.22(CH), 112.37(C), 116.47(C), 117.32(CH), 121.49(CH), 125.41(CH), 132.01 (CH), 142.04(CH), 143.54(CH), 144.54(C), 152.56(C), 157.36(C), 158.51(C). Anal. Calcd. for $C_{15}H_8O_4$: C, 71.43; H, 3.20%. Found: C, 71.40; H, 3.27%. MS m/z : 252.0 (M^+).

3-(Furan-2-yl)-6-methyl-4H-furo[3,2-c]chromen-4-one (3b). IR spectrum, ν_{max} , cm^{-1} : 3150 & 2921 (aromatic C-H), 1749 (C=O, δ -lactone), 1624 (C=C, aromatic) cm^{-1} ; 1H NMR (DMSO- d_6) δ , ppm (J , Hz): 2.44 (3H, s, CH_3), 6.65 (1H, q, J =1.6 Hz, Ar-H), 7.38 (2H, m, Ar-H), 7.54 (1H, d, J 7.6 Hz, Ar-H), 7.80 (2H, distorted doublet, J 6.8 Hz, Ar-H), 8.52 (1H, s, Ar-H); ^{13}C NMR ($CDCl_3$ & DMSO- d_6) δ , ppm: 15.49(CH_3), 105.98(C), 110.87(CH), 111.62(CH), 116.02(C), 118.55(CH), 124.33(CH), 125.83(C), 132.45(CH), 141.25(CH), 142.75(CH), 143.13(C), 144.12(C), 150.45(C), 156.73(C), 158.39(C). Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79%. Found: C, 72.22; H, 3.80%. MS m/z : 266.0 (M^+).

3-(Furan-2-yl)-8-methyl-4H-furo[3,2-c]chromen-4-one (3c). IR spectrum, ν_{max} , cm^{-1} : 3155 & 2922 (aromatic C-H), 1737 (C=O, δ -lactone), 1629 (C=C, aromatic) cm^{-1} . 1H NMR (DMSO- d_6) δ , ppm (J , Hz): 2.42 (3H, s, CH_3), 6.64 (1H, q, J 1.6 Hz, Ar-H), 7.38 (1H, d, J 3.2 Hz, Ar-H), 7.44 (2H, distorted triplet, J 8.8 Hz, Ar-H), 7.75 (1H, s, Ar-H), 7.79 (1H, s, Ar-H), 8.51 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$ & DMSO- d_6) δ , ppm: 20.40(CH_3), 106.09(C), 110.86(CH), 111.47(CH), 111.57(C), 116.16(C), 116.43(CH), 120.38(CH), 132.15(CH), 134.20(C), 140.89(CH), 142.46(CH), 144.10(C), 150.28(C), 156.87(C), 157.97(C). Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 72.21; H, 3.81%. MS m/z : 266 (M^+).

3-(Furan-2-yl)-8-chloro-4H-furo[3,2-c]chromen-4-one (3d). IR spectrum, ν_{max} , cm^{-1} : 3141 & 2921 (aromatic C-H), 1741 (C=O, δ -lactone), 1647 (C=C, aromatic) cm^{-1} . 1H NMR (DMSO- d_6) δ , ppm (J , Hz): δ (ppm) 6.65 (1H, q, J 1.6 Hz, Ar-H), 7.37 (1H, d, J 3.2 Hz, Ar-H), 7.61 (1H, d, J 8.8 Hz, Ar-H), 7.70 (1H, dd, J 9.2 and 2.4 Hz, Ar-H), 7.80 (1H, d, J 1.2 Hz, Ar-H), 8.02 (1H, d, J 2.4 Hz, Ar-H), 8.59 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$ & DMSO- d_6) δ , ppm: 106.98(C), 111.03(CH), 111.51(CH), 113.20(C), 116.32(C), 118.67(CH), 120.14(CH), 129.19(C), 130.97(CH), 141.61(CH), 142.62(CH), 143.78(C), 150.55(C), 156.30(C), 156.70(C). Anal. Calcd. for $C_{15}H_7ClO_4$: C, 62.85; H, 2.46%. Found: C, 62.88; H, 2.47%. MS m/z : 286.0 (M^+).

3-(Benzofuran-2-yl)-4H-furo[3,2-c]chromen-4-one (4a). IR spectrum, ν_{max} , cm^{-1} : 3162 & 3060 (aromatic C-H), 1739 (C=O, δ -lactone), 1624 (aromatic C=C) cm^{-1} . 1H NMR ($CDCl_3$) δ , ppm (J , Hz): 7.27-7.29 (2H, m, Ar-H), 7.35 (1H, td, J 8.0 and 1.6 Hz, Ar-H), 7.45 (1H, d, J 8.8 Hz, Ar-H), 7.49-7.55 (2H, m, Ar-H), 7.67 (1H, d, J 7.6 Hz, Ar-H), 7.93 (1H, d, J 2.4 Hz, Ar-H), 8.01 (1H, s, Ar-H), 8.23 (1H, s, Ar-H). ^{13}C NMR (DMSO- d_6) δ , ppm: 107.59(CH), 111.25(CH), 112.42(C), 116.35(C), 117.39(CH), 121.59(CH), 122.03(CH), 123.71(CH), 125.50(CH), 125.70(CH), 128.88(C), 132.22(CH), 134.54(C), 143.85(CH), 146.89(C), 152.80(C), 154.51(C), 157.36(C), 159.06(C). Anal. Calcd. for $C_{19}H_{10}O_4$: C, 75.49; H, 3.33%. Found: C, 75.55; H, 3.90%. MS m/z : 302.0 (M^+).

3-(Benzofuran-2-yl)-6-methyl-4H-furo[3,2-c]chromen-4-one (4b). IR spectrum, ν_{max} , cm^{-1} : 3154 & 3060 (aromatic C-H), 1737 (C=O, δ -lactone), 1620 (C=C, aromatic) cm^{-1} . 1H NMR ($CDCl_3$) δ , ppm (J , Hz): 2.56 (3H, s, CH_3), 7.24 - 7.34 (3H, m, Ar-H), 7.42 (1H, d, J 7.2 Hz, Ar-H), 7.49 (1H, d, J 7.6 Hz, Ar-H), 7.67 (1H, d, J 7.6 Hz, Ar-H), 7.78 (1H, d, J 7.6 Hz, Ar-H), 8.01 (1H, s, Ar-H), 8.17 (1H, s, Ar-H). ^{13}C NMR (DMSO- d_6) δ , ppm: 15.53(CH_3), 106.96(CH), 110.78(CH), 115.77(C), 116.93(C), 118.76(CH), 121.64(CH), 123.29(CH), 124.59(CH), 125.28(CH), 125.92(C), 127.39(C), 128.28(C), 132.80(CH), 143.39(CH), 146.49(C), 150.43(C), 153.82(C), 156.71(C), 158.92(C). Anal. Calcd. for $C_{20}H_{12}O_4$: C, 75.94; H, 3.82%. Found: C, 75.89; H, 3.80%. MS m/z : 316.0 (M^+).

3-(Benzofuran-2-yl)-8-methyl-4H-furo[3,2-c]chromen-4-one (4c). IR spectrum, ν_{\max} , cm^{-1} : 3154 & 2922 (aromatic C-H), 1735 (C=O, δ -lactone), 1629 (aromatic C=C) cm^{-1} . ^1H NMR (DMSO- d_6) δ , ppm (J , Hz): 2.44 (3H, s, CH_3), 7.29 (1H, t, J 8.0 Hz, Ar-H), 7.37 (1H, td, J 7.8 and 1.6 Hz, Ar-H), 7.50 (2H, d, J 0.8 Hz, Ar-H), 7.61 (1H, dd, J 8.0 and 0.8 Hz, Ar-H), 7.76 (1H, d, J 7.2 Hz, Ar-H), 7.81 (1H, s, Ar-H), 7.90 (1H, s, Ar-H), 8.77 (1H, s, Ar-H). ^{13}C NMR (DMSO- d_6) δ , ppm: 20.77(CH_3), 107.56(CH), 111.23(CH), 112.08(C), 116.34(C), 117.15(CH), 121.08(CH), 122.00(CH), 123.69(CH), 125.66(CH), 128.88(C), 133.11(CH), 135.07(C), 143.72(C), 146.92(C), 151.02(C), 154.51(C), 157.52(C), 159.05(C). Anal. Calcd. for $\text{C}_{20}\text{H}_{12}\text{O}_4$: C, 75.94; H, 3.82. Found: C, 75.88; H, 3.81%. MS m/z : 316.0 (M^+).

3-(Benzofuran-2-yl)-8-chloro-4H-furo[3,2-c]chromen-4-one (4d). IR spectrum, ν_{\max} , cm^{-1} : 3121 & 3047 (aromatic C-H), 1735 (C=O, δ -lactone), 1619 (aromatic C=C) cm^{-1} . ^1H NMR (DMSO- d_6) δ , ppm (J , Hz): 7.29 (1H, t, J 7.6 Hz, Ar-H), 7.37 (1H, td, J 8.0 and 1.2 Hz, Ar-H), 7.63 (2H, dd, J 11.6 and 8.4, Ar-H), 7.71-7.77 (2H, m, Ar-H), 7.89 (1H, s, Ar-H), 8.07 (1H, d, J 2.4, Ar-H), 8.83 (1H, s, Ar-H). ^{13}C NMR (DMSO- d_6) δ , ppm: 107.71(CH), 107.92(C), 111.34(CH), 113.83(C), 116.37(C), 119.54(CH), 120.99(CH), 122.22(CH), 123.86(CH), 125.90(CH), 128.78(C), 129.59(C), 131.91(CH), 144.49(CH), 146.71(C), 151.31(C), 154.39(C), 155.20(C), 157.19(C). Anal. Calcd. for $\text{C}_{19}\text{H}_9\text{ClO}_4$: C, 67.77; H, 2.69%. Found: C, 67.74; H, 2.66%. MS m/z : 336.0 (M^+).

Supplementary Material

Supplementary material related to this article, including characterization data like Infrared spectra, Nuclear Magnetic Resonance (^1H , ^{13}C NMR and DEPT-90) and Mass spectra figures for synthesized compounds **2a-d**, **3a-d** and **4a-d** reported in this article is available in the online version of the text.

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References

1. Wang, L.; Wu, H.-L.; Yin, X.-L.; Hu, Y.; Gu, H.-W.; Yu, R.-Q. *Acta Part A Mol. Biomol. Spectrosc.* **2017**, *170*, 104–110.
<https://doi.org/10.1016/j.saa.2016.07.018>
2. Vilar, S.; Quezada, E.; Santana, L.; Uriarte, E.; Yanez, M.; Fraiz, N.; Alcaide, C.; Cano, E.; Orallo, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 257-261.
<https://doi.org/10.1016/j.bmcl.2005.10.013>
3. D. Yim, P. R. Singh, C. Agarwal, S. Lee, H. Chi, R. A. *Cancer Res.* **2005**, *65*, 1035–1044.
4. Ostrov, D. A.; Hernandez Prada, J. A.; Corsino, P. E.; Finton, K. A.; Le, N.; Rowe, T. C. *Antimicrob. Agents Chemother.* **2007**, *51*, 3688–3698.
<https://doi.org/10.1128/AAC.00392-07>

5. Zhang, Y.; Zou, B.; Chen, Z.; Pan, Y.; Wang, H.; Liang, H.; Yi, X. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6811–6815.
<https://doi.org/10.1016/j.bmcl.2011.09.029>
6. Curini, M.; Epifano, F.; Maltese, F.; Marcotullio, M. C.; Gonzales, S. P.; Rodriguez, *Aust. J. Chem.* **2003**, *56*, 59–60.
<https://doi.org/10.1071/CH02177>
7. Manvar, A.; Bavishi, A.; Radadiya, A.; Patel, J.; Vora, V.; Dodia, N.; Rawal, K.; Shah, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4728–4731.
<https://doi.org/10.1016/j.bmcl.2011.06.074>
8. Bullock, S. J.; Felton, C. E.; Fennessy, R. V.; Harding, L. P.; Andrews, M.; Pope, S. J. A.; Rice, C. R.; Riis-Johannessen, T. *Dalton Trans*, **2009**, *47*, 10570-10573.
<https://doi.org/10.1039/b913103e>
9. Traven, V. F.; Manaev, A. V.; Bochkov, A. Y.; Chibisova, T. A.; Ivanov, I. V. *Russ. Chem. Bull.* **2012**, *61*, 1342–1362.
<https://doi.org/10.1007/s11172-012-0179-2>
10. Parikh, P. H.; Timaniya, J. B.; Patel, M. J.; Patel, K. P. *Med. Chem. Res.* **2020**, *29*, 538-548.
<https://doi.org/10.1007/s00044-020-02505-8>
11. Belal, M.; Das, D. K.; Khan, A. T. *Synthesis*, **2015**, *47*, 1109-1116.
<https://doi.org/10.1055/s-0034-1380131>
12. Ahadi, S.; Zolghadr, M.; Khavasi, H. R.; Bazgir, A. *Org. Biomol. Chem* **2013**, *11*, 279-286.
<https://doi.org/10.1039/c2ob26203g>
13. Lin, C.-H.; Yang, D.-Y. *Org. Lett.* **2013**, *15*, 2802–2805.
<https://doi.org/10.1021/ol401138q>
14. Mohammadi Ziarani, G.; Moradi, R.; Ahmadi, T.; Gholamzadeh, P. *Mol. Divers.* **2019**, *23*, 1029-1064.
<https://doi.org/10.1007/s11030-019-09918-7>
15. Tan, G.; You, Q.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 6309–6313.
<https://doi.org/10.1002/anie.201802539>
16. Dey, A.; Ali, M. A.; Jana, S.; Samanta, S.; Hajra, A. *Tetrahedron Lett.* **2017**, *58*, 313–316.
<https://doi.org/10.1016/j.tetlet.2016.12.010>
17. Belal, M.; Khan, A. T. *RSC Adv.* **2016**, *6*, 18891–18894.
<https://doi.org/10.1039/C5RA27993C>
18. Belal, M.; Khan, A. T. *RSC Adv.* **2015**, *5*, 104155–104163.
<https://doi.org/10.1039/C5RA20405D>
19. Peroutka, R.; Schulzová, V.; Botek, P.; Hajslova, J. *J. Sci. Food Agric.* **2007**, *87*, 2152–2163.
<https://doi.org/10.1002/jsfa.2979>
20. McNeely, W.; Goa, K. L. *Drugs* **1998**, *56*, 667–690.
<https://doi.org/10.2165/00003495-199856040-00015>
21. V. Lipeeva, A.; V. Khvostov, M.; S. Baev, D.; M. Shakirov, M.; G. Tolstikova, T.; E. Shults, E. *Med. Chem. (Los. Angeles)*. **2016**, *12*, 674–683.
<https://doi.org/10.2174/1573406412666160129105115>
22. Zhang, G.; Zhang, Y.; Yan, J.; Chen, R.; Wang, S.; Ma, Y.; Wang, R. *J. Org. Chem.* **2012**, *77*, 878–888.
<https://doi.org/10.1021/jo202020m>

23. Song, P.-P.; Zhao, J.; Liu, Z.-L.; Duan, Y.-B.; Hou, Y.-P.; Zhao, C.-Q.; Wu, M.; Wei, M.; Wang, N.-H.; Lv, Y.; et al. *Pest Manag. Sci.* **2017**, *73*, 94–101.
<https://doi.org/10.1002/ps.4422>
24. Symeonidis, T.; Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E. *Eur. J. Med. Chem.* **2009**, *44*, 5012–5017.
<https://doi.org/10.1016/j.ejmech.2009.09.004>
25. Panno, M. L.; Giordano, F. *World J. Clin. Oncol.* **2014**, *5*, 348–358.
<https://doi.org/10.5306/wjco.v5.i3.348>
26. Wrzesniok, D.; Beberok, A.; Rok, J.; Delijewski, M.; Hechmann, A.; Oprzondek, M.; Rzepka, Z.; Bacler-Żbikowska, B.; Buszman, E. *Int. J. Radiat. Biol.* **2017**, *93*, 734–739.
<https://doi.org/10.1080/09553002.2017.1297903>
27. Rajabi, M.; Hossaini, Z.; Khalilzadeh, M. A.; Datta, S.; Halder, M.; Mousa, S. A. *J. Photochem. Photobiol. B Biol.* **2015**, *148*, 66–72.
<https://doi.org/10.1016/j.jphotobiol.2015.03.027>
28. Bondock, S.; Khalifa, W.; Fadda, A. A. *Eur. J. Med. Chem.* **2011**, *46*, 2555–2561.
<https://doi.org/10.1016/j.ejmech.2011.03.045>
29. Lakhani, D. M.; Deshpande, A. S. *J. Appl. Pharm. Sci.* **2014**, *4*, 101–105.
<https://doi.org/10.7324/JAPS.2014.41118>
30. Ortonne, J.-P. *Clin. Dermatol.* **1989**, *7*, 120–135.
[https://doi.org/10.1016/0738-081X\(89\)90062-X](https://doi.org/10.1016/0738-081X(89)90062-X)
31. Bordin, F.; Dall'acqua, F.; Guiotto, A. Angelicins, *Pharmacol. Ther.* **1991**, *52*, 331–363.
[https://doi.org/10.1016/0163-7258\(91\)90031-G](https://doi.org/10.1016/0163-7258(91)90031-G)
32. Jiang, Z.; Xiong, J. *Cell Biochem. Biophys.* **2014**, *70*, 1075–1081.
<https://doi.org/10.1007/s12013-014-0025-2>
33. Khalilzadeh, M. A.; Hossaini, Z.; Charati, F. R.; Hallajian, S.; Rajabi, M. *Mol. Divers.* **2011**, *15*, 445–450.
<https://doi.org/10.1007/s11030-010-9264-3>
34. Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732–4735.
<https://doi.org/10.1021/jo800439y>
35. Al-Sehemi, A. G.; El-Gogary, S. R. *Chinese J. Chem.* **2012**, *30*, 316–320.
<https://doi.org/10.1002/cjoc.201180483>
36. Zhou, H.; Deng, X.; Ma, Z.; Zhang, A.; Qin, Q.; Tan, R. X.; Yu, S. *Org. Biomol. Chem.* **2016**, *14*, 6065–6070.
<https://doi.org/10.1039/C6OB00768F>
37. Kenchappa, R.; Bodke, Y. D.; Telkar, S.; Nagaraja, O. *Russ. J. Gen. Chem.* **2017**, *87*, 2027–2038.
<https://doi.org/10.1134/S1070363217090195>
38. Kenchappa, R.; Bodke, Y. D.; Peethambar, S. K.; Telkar, S.; Bhovi, V. K. *Med. Chem. Res.* **2013**, *22*, 4787–4797.
<https://doi.org/10.1007/s00044-013-0494-7>
39. Sunitha, V.; Kishore Kumar, A.; Shankar, B.; Anil Kumar, A.; Krishna, T. M.; Lincoln, C. A.; Pochampalli, J. *Russ. J. Gen. Chem.* **2017**, *87*, 322–330.
<https://doi.org/10.1134/S1070363217020281>
40. Lee, H.-K.; Chan, K.-F.; Hui, C.-W.; Yim, H.-K.; Wu, X.-W.; Wong, H. N. C. *Pure Appl. Chem.* **2005**, *77*, 139–143.
<https://doi.org/10.1351/pac200577010139>

41. Alvarez, C.; Alvarez, R.; Corchete, P.; Perez-Melero, C.; Pelaez, R.; Medarde, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3417–3420.
<https://doi.org/10.1016/j.bmcl.2007.03.082>
42. Patel, M.; Patel, K. *Heterocycl. Commun.* **2019**, *25*, 146–151.
<https://doi.org/10.1515/hc-2019-0024>
43. Vardhan, K. H.; Kumar, P. S.; Panda, R. C. *J. Mol. Liq.* **2019**, 111-197.
<https://doi.org/10.1016/j.molliq.2019.111197>
44. Kaushal P. Patel. *Arkivoc* **2013**, (iii), 14–23.
<https://doi.org/http://dx.doi.org/10.3998/ark.5550190.0014.302>
45. Li, J. *J. Am. Chem. Soc.* **2009**, *131*, 18572-18572.
<https://doi.org/10.1021/ja9097912>
46. Kaneria, A. R.; Giri, R. R.; Bhila, V. G.; Prajapati, H. J.; Brahmabhatt, D. I. *Arab. J. Chem.* **2017**, *10*, S1100–S1104.
<https://doi.org/10.1016/j.arabjc.2013.01.017>
47. He, M.; Yan, Z.; Wang, W.; Zhu, F.; Lin, S. *Tetrahedron Lett.* **2018**, *59*, 3706–3712.
<https://doi.org/10.1016/j.tetlet.2018.09.007>

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