

Synthesis of Substituted-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates

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ABSTRACT

A novel series of substituted-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates (5a-h) have been synthesised in satisfactory yields in presence of Caesium carbonate and dry *N,N*-dimethyl formamide by reacting with the 9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid (3) with various phenyl-1,2,4-oxadiazoles (4a-h) for 8–10 h at room temperature and their structures were confirmed by ¹H NMR, ¹³C NMR, IR and Mass spectral analyses and they were good agreement with proposed structures.

Key words: Caesium carbonate, *N*'-hydroxybenzamidines, Phenyl-1,2,4-oxadiazoles, Vilsmeier-Haack-Arnold reaction.

1. INTRODUCTION

N-possessing heterocycles exhibit efficient and various biological activities such as anticancer [1], treating Cystic fibrosis [2], anti-HIV [3], Obesity [4], inflammation [5] and infections, [6] etc. Among the different types of the nitrogen heterocyclic compounds specifically, oxadiazoles are very important in Medicinal Chemistry, Agro-chemistry (pesticides), Polymer and Material Science. Oxadiazoles with a combination of two and one carbon, nitrogen and oxygen atoms, respectively. Moreover, the oxadiazole moiety has special properties as good ligand binding efficiency [7], linking various substitutes with proper orientation [8] and modulation of positions to periphery side [9] oxadiazole regioisomers [10] where variation of thermodynamics properties can be obtained by influencing active site. Oxadiazole moieties were present in various biological active compounds, such as Zibotentan (1), Ataluren (2), and Raltegravir (3).

In this communication, herewith we are reporting hitherto unreported synthesis of substituted-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate derivatives (5a-h) by reacting with phenyl-1,2,4-oxadiazole (4) and 9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid (3) in the presence of caesium carbonate at room temperature (Scheme 1).

2. RESULTS AND DISCUSSION

In continuation of our research on the development of new biological active compounds, a novel series of substituted-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates (5a-h) were synthesized by following Scheme 1.

A key intermediate of 9-Chloro-6,7-dihydro-5H-benzocyclohepten-8-carbaldehyde (2) was synthesized in 82% yield with 2,3-dimethyl-6,7,8,9-tetrahydro benzocyclohepten-5-one (1) [11] by Vilsmeier-Haack-Arnold reaction treating with POCl₃, dimethylformamide. Subsequently benzocyclohepten-8-carbaldehyde (2) was oxidized to 9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid (3) using hydrogen peroxide and buffer solution (sodium dihydrogen sulphate and sodium chlorite in H₂O).

Substituted phenyl-1,2,4-oxadiazoles (4a-h) has been synthesized by following modified procedure [12]. The reaction between *N*'-hydroxy benzamidines (which were obtained by the reaction of various benzonitrile with NH₂OH.HCl in presence of NaOH for 2–3 h in methanol at reflux temperature) and chloroacetyl chloride with a pinch of triethyl amine in benzene solvent for 2–3 h at reflux temperature substituted phenyl-1,2,4-oxadiazoles (4a-h) has been obtained in quantitative yields.

Finally, desired substituted-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates (5a-h) have been obtained in good yields by the reaction of various phenyl-1,2,4-oxadiazoles (4a-h) with 9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid (3) in presence of dry *N,N*-dimethylformamide and caesium carbonate for 8–10 h at room temperature (Scheme 1) and targeted structures were confirmed by ¹H NMR, ¹³C NMR, IR and Mass spectral analysis. Spectral analysis were good accord with the obtained structures.

All the newly synthesized derivatives 5a-h were confirmed by using ¹H NMR, IR and Mass spectroscopic methods. All synthesized compounds spectral data were in accord with the structures. For example, compound 5c was characterized by its ¹H NMR spectrum which shows characteristic doublet corresponding to bromo substituted aromatic4-protons of the oxadiazole ring at 7.55 and 7.98 ppm and O-CH₂-protons of oxadiazole coupled 9-chloro-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid appeared at δ 5.55 ppm as singlet and which was further verified by ESI-MS having a mass ESI-MS: *m/z* = 487 [M+H] and 489 [M+2]⁺ suggesting that the molecular formula of

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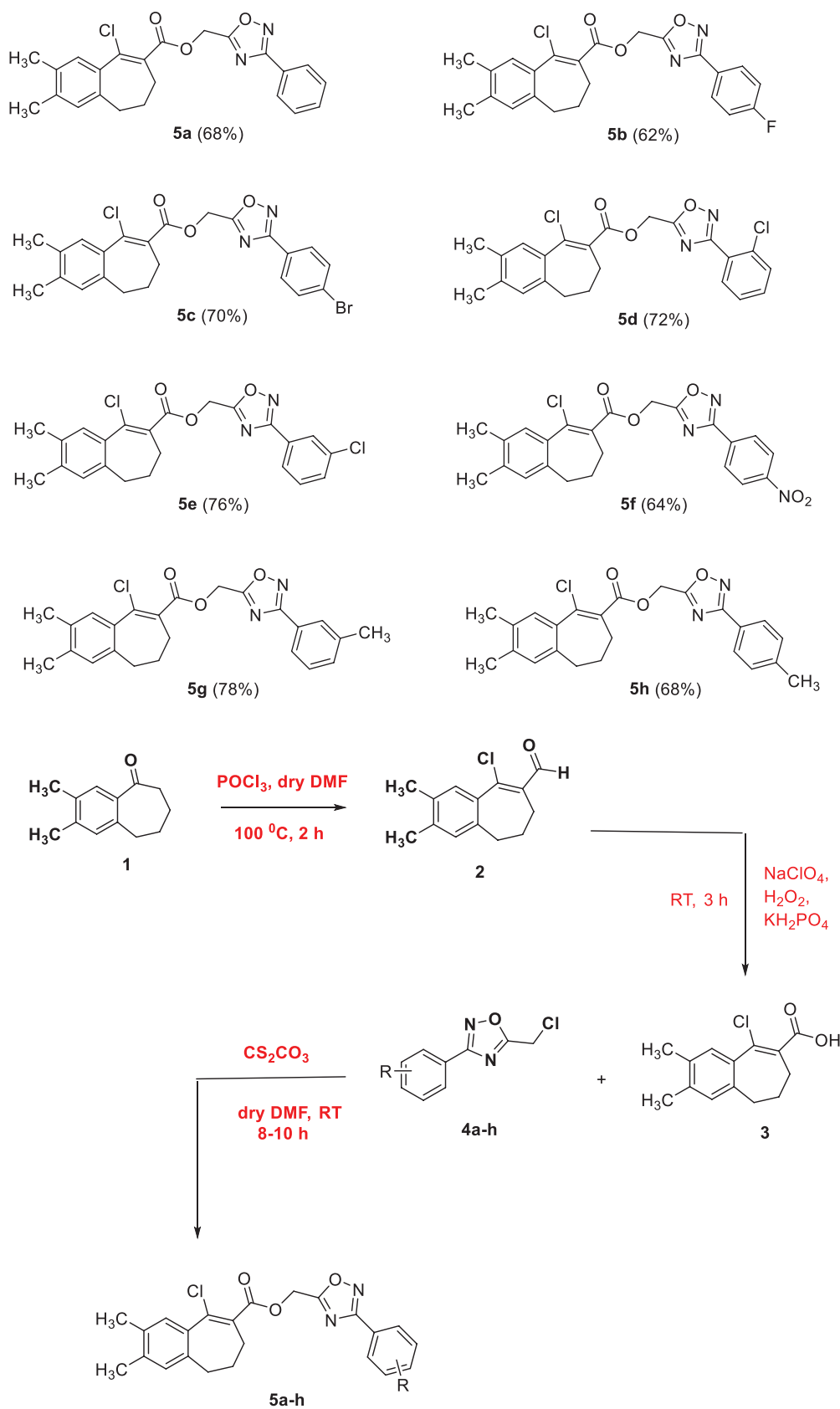
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AQ4 Scheme 1: ???

$\text{C}_{23}\text{H}_{20}\text{BrClN}_2\text{O}_3$. Moreover, characteristic absorption bands at 2946, 1737, 1590, 1402 cm^{-1} in the IR spectra which corresponded to C=N, C=C, C=O and C-N respectively.

3. EXPERIMENTAL

To know the melting points of the compounds Stuart-smp 20 melting point apparatus was used. Shimadzu FTIR 8400-S (KBr pellets) was

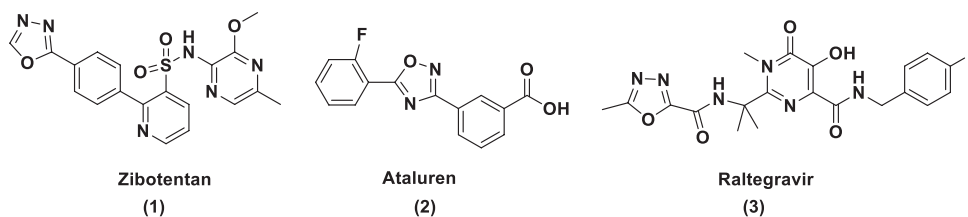


Figure 1: Various biologically active structures having oxadiazole ring system.

used to record IR spectra. 100b MHz for ^{13}C and 400 MHz for ^1H , Bruker Avance were used to record NMR spectra and Fisons VG Platform II and Micro mass Q-TOF Ultima Global 7 (ESI was used to record Mass spectra).

3.1. 9-Chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carbaldehyde (2)

In a round bottom flask containing *N,N*-dimethylformamide (6 mL) phosphorus oxychloride (3 eq) was added at 0°C and stirred for 10 min. 2,3-Dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (1, 6.2 mmol) was added drop wise to the above mixture and stirred for 15 min. at same temperature and 3 h at 80°C . Progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature and poured on crushed ice. Then, neutralized with 20% sodium bicarbonate solution, extracted with ethyl acetate (3×100 mL), brine solution (2×50 mL) and water (3×100 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc: Hexane 2:8 as eluent to get 9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carbaldehyde (2). Yield: 74%, pale yellow solid with m. p. $61\text{--}62^\circ\text{C}$. IR (KBr): ν 2940, 1669 cm^{-1} . ^1H NMR (300MHz, CDCl_3): δ 2.05–2.18 (m, 2H, $-\text{CH}_2-$), 2.19–2.29 (t, $J=7.17$ Hz, 2H, $-\text{CH}_2-$), 2.30 (s, 6H, $-\text{CH}_3$), 2.50–2.58 (t, $J=7.01$ Hz, 2H, $-\text{CH}_2-$), 7.01 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 10.40 (s, 1H, $-\text{CHO}$). ESI-MS: $m/z=235$ [M+H] and 237 [M+2].

3.2. 9-Chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid (3)

To a round bottom flask containing acetonitrile (10 mL), 9-Chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carbaldehyde (2, 1eq.) was added at room temperature and stirred for 5 min. at room temperature, Then, freshly prepared buffer solution was added and stirred for 3 h at room temperature. The reaction mixture was poured on crushed ice, neutralized with 32% hydrochloric acid, extracted with ethyl acetate (3×100 mL), washed with brine solution (2×50 mL) and water (3×100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain corresponding carboxylic acid (3) in quantitative yield. White solid with m. p. $140\text{--}142^\circ\text{C}$. IR (KBr): ν 3117, 2930, 1679 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.15–2.20 (m, 4H, $-\text{CH}_2-$), 2.25 (s, 6H, 2x- CH_3), 2.55–2.65 (t, 2H, $-\text{CH}_2-$), 7.00 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H). ESI-MS: $m/z=251$ [M+H].

3.3. General procedure for substituted-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates (13a-h)

9-Chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylic acid (3, 1eq) and (5-chloromethyl)-3-phenyl-1,2,4-oxadiazole (5a, 1.2 eq) were stirred at room temperature for 8–10 h in presence of Caesium carbonate (3eq) and dry *N,N'*-dimethylformamide (5 mL). Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with

ethyl acetate (3×100 mL), brine solution (2×50 mL) and water (3×100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to get following derivatives:

3.3.1. (3-Phenyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5a)
Yield: 68%, m. p. $93\text{--}95^\circ\text{C}$. IR (KBr): ν 2925, 1741, 1608, 1443, 1282 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.18–2.25 (m, 2H, $-\text{CH}_2-$), 2.30 (s, 6H, 2x- CH_3), 2.35–2.38 (t, 2H, $-\text{CH}_2-$), 2.61–2.65 (t, 2H, $-\text{CH}_2-$), 5.35 (s, 2H, $-\text{OCH}_2-$), 7.00 (s, 1H, Ar-H), 7.15–7.28 (m, 5H, Ar-H), 7.40 (s, 1H, Ar-H). ESI-MS m/z : 409[M+H] and 411[M+2] for $\text{C}_{23}\text{H}_{21}\text{ClN}_2\text{O}_3$.

3.3.2. (3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5b)

Yield: 62%, m. p. $142\text{--}144^\circ\text{C}$. IR (KBr) ν/cm^{-1} : ν 2923, 1734, 1603, 812 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.18–2.40 (m, 2H, $-\text{CH}_2-$), 2.28 (s, 6H, 2x- CH_3), 2.29–2.35 (t, 2H, $-\text{CH}_2-$), 2.58–2.65 (t, 2H, $-\text{CH}_2-$), 5.52 (s, 2H, $-\text{OCH}_2-$), 7.00 (s, 1H, Ar-H), 7.18 (d, 2H, Ar-H), 7.39 (s, 1H, Ar-H), 8.10 (d, 2H, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ 19.06, 19.24, 27.93, 29.36, 30.68, 34.07, 56.42, 115.69, 115.90, 127.34, 129.334, 129.42, 129.46, 129.64, 134.64, 135.03, 137.44, 138.16, 138.64, 165.51, 167.4, 173.78. ESI-MS: $m/z = 427$ [M+H] and 429 [M+2] for $\text{C}_{23}\text{H}_{20}\text{ClFN}_2\text{O}_3$.

3.3.3. (3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5c)

Yield: 70%, m. p. $139\text{--}141.8^\circ\text{C}$. IR (KBr) ν/cm^{-1} : ν 2946, 1737, 1172, 842 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.19–2.29 (m, 2H, $-\text{CH}_2-$), 2.30 (s, 6H, 2x- CH_3), 2.31–2.32 (t, 2H, $-\text{CH}_2-$), 2.60–2.64 (t, 2H, $-\text{CH}_2-$), 5.51 (s, 2H, $-\text{OCH}_2-$), 7.00 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.62 (d, 2H, Ar-H), 7.98 (d, 2H, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ 19.07, 19.74, 28.56, 31.31, 34.69, 57.03, 128.06, 129.29, 130.10, 130.27, 132.51, 135.27, 138.07, 139.29, 166.13, 168.19, 174.55. ESI-MS: $m/z = 487$ [M+H] and 489 [M+2] for $\text{C}_{23}\text{H}_{20}\text{BrClN}_2\text{O}_3$.

3.3.4. (3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5d)

Yield: 72%, Pale yellow liquid. IR (KBr) ν/cm^{-1} : ν 2955, 2921, 1457, 1376, 876 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.31–2.35 (m, 2H, $-\text{CH}_2-$), 2.35 (s, 6H, 2x- CH_3), 2.39–2.49 (t, 2H, $-\text{CH}_2-$), 2.61–2.74 (t, 2H, $-\text{CH}_2-$), 5.51 (s, 2H, $-\text{OCH}_2-$), 7.00 (s, 1H, Ar-H), 7.34 (s, 1H, Ar-H), 7.90–8.01 (m, 4H, Ar-H). ESI-MS: $m/z = 443$ [M+H] and 445 [M+2] for $\text{C}_{23}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_3$.

3.3.5. (3-(3-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5e)

Yield: 76%, m. p. $102.3\text{--}102.8^\circ\text{C}$. IR (KBr) ν/cm^{-1} : ν 2954, 2926, 1455, 1378, 876 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.30–2.33 (m, 2H, $-\text{CH}_2-$), 2.32 (s, 6H, 2x- CH_3), 2.38–2.46 (t, 2H, $-\text{CH}_2-$), 2.60–2.73 (t, 2H, $-\text{CH}_2-$), 5.50 (s, 2H, $-\text{OCH}_2-$), 7.00 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.88–8.00 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ 19.02, 19.29, 27.89, 30.64, 34.03, 56.42, 127.13, 128.51, 129.42, 129.59,

131.02, 165.51, 167.4, 173.78. ESI-MS: $m/z = 443$ [M+H] and 445 [M+2] for $C_{23}H_{20}Cl_2N_2O_3$.

3.3.6. (3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5f)

Yield: 64%, m. p. 127–130.8°C. IR (KBr) ν/cm^{-1} : ν 2946, 1673, 1286, 1192 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$): δ 2.23–2.49 (m, 2H, -CH₂-), 2.30 (s, 6H, 2x-CH₃), 2.32–2.39 (t, 2H, -CH₂-), 2.62–2.70 (t, 2H, -CH₂-), 5.59 (s, 2H, -OCH₂-), 7.01 (s, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 8.10 (d, 2H, Ar-H), 8.13 (d, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.70, 19.69, 19.70, 19.96, 28.55, 31.31, 34.60, 128.60, 130.08, 130.22, 165.41, 167.4, 175.78. ESI-MS: $m/z = 454$ [M+H] and 456 [M+2] for $C_{23}H_{20}ClN_3O_5$.

3.3.7. (3-(*m*-Tolyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5g)

Yield: 78%, Semi solid. IR (KBr) ν/cm^{-1} : ν 2930, 1700, 1600, 1288, 886 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 2.22–2.32 (m, 2H, -CH₂-), 2.35 (s, 6H, 2x-CH₃), 2.40–2.49 (over lapped t and s, of 2H, -CH₂- and 3H, Ar-CH₃), 2.61–2.70 (t, 2H, -CH₂-), 5.09 (s, 2H, -OCH₂-), 7.00 (s, 1H, Ar-H), 7.35–7.44 (m, 4H, Ar-H), 7.49 (s, 1H, Ar-H). ESI-MS: $m/z = 423$ [M+H] and 425 [M+2] for $C_{24}H_{23}ClN_3O_3$.

3.3.8. (3-(*p*-Tolyl)-1,2,4-oxadiazol-5-yl)methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylate (5h)

Yield: 68%, m. p. 104–106.8°C. IR (KBr) ν/cm^{-1} : ν 2931, 2861, 1701, 1589, 1290, 1180, 1114 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$): δ 2.16–2.32 (m, 2H, -CH₂-), 2.28 (s, 6H, 2x-CH₃), 2.29–2.31 (t, 2H, -CH₂-), 2.41 (s, 3H, Ar-CH₃), 2.59–2.65 (t, 2H, -CH₂-), 5.52 (s, 2H, -OCH₂-), 7.00 (s, 1H, Ar-H), 7.30 (d, 2H, Ar-H), 7.39 (s, 1H, Ar-H), 8.00 (d, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.38, 19.65, 28.25, 31.01, 34.38, 56.81, 137.27, 127.42, 129.59, 138.92, 134.93, 140.66, 141.78, 144.88, 148.62, 173.76. ESI-MS: $m/z = 423$ [M+H] and 425 [M+2] for $C_{24}H_{23}ClN_3O_3$.

4. CONCLUSION

A series of substituted (3-phenyl-1,2,4-oxadiazol-5-yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates (5a-h) have been synthesised in satisfactory yields and their structures were confirmed by 1H NMR, ^{13}C NMR, IR and Mass spectral analyses which were good agreement with proposed structures.

5. ACKNOWLEDGMENT

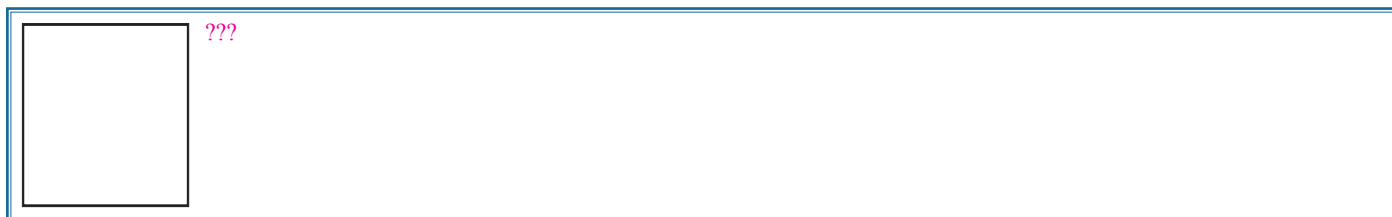
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