

Synthesis and Antimicrobial Evaluation of Some Substituted-3-Aryl -2,3,4,5,6,7-hexahydro-1H-inden-1-one

MANJUNATH MOGER¹, DARSHAN RAJ C GOVINDRAJU²,
RAMA MOHAN HINDUPUR¹ and HARI NARAYAN PATI^{*1}

¹Advinus Therapeutics Ltd., 21 & 22, Phase II, Peenya Industrial Area, Bangalore-560058, Karnataka, India

²Department of Bio-Medicinal Research, Vidya Herbs Pvt. Ltd., Bangalore-562106, Karnataka, India

hari.pati@advinus.com

Received 16 April 2014 / Accepted 2 May 2014

Abstract: Synthesis of new cyclopentenone derivatives by reacting 1-acetyl-1-cyclohexene with various aromatic and heteroaromatic aldehydes is reported. All the new cyclopentenone derivatives were characterized by ¹H, ¹³C NMR, IR and mass spectral data, and were further screened for their antimicrobial activity. Most of the compounds showed comparable activities with standard drug ciprofloxacin and in particular, compounds **3d**, **3f**, **3g** and **3j** showed excellent activity against all the four bacterial strains.

Keywords: Cyclopentenone, Nazarov reaction, Acetic acid, Anti-microbial activity

Introduction

2-Cyclopentenones are five membered carbocycles consisting of α,β -unsaturated ketone system. Cyclopentenone and its derivatives are important motifs in synthetic organic chemistry as they are useful key intermediates in total synthesis^{1,2} of natural products like methylenomycin B³, a natural cyclopentanoid antibiotic, ligands of the 5HT_{1D} serotonin receptors⁴, prostaglandin⁵, etc.

Cyclopentenones contain a highly electrophilic keto ethylenic group (-CO-CH=CH-) which could be responsible for broad spectrum of pharmacological activities like anti-inflammatory⁶, anti-microbial⁷, anti-mitotic⁸, cytotoxic⁹ and anti-pigment¹⁰ activities. In continuation of our work on cyclopentenone derivatives¹¹, herein we wish to report synthesis of new class of aryl substituted and hetero aryl cyclopentenone derivatives and their antimicrobial activities.

Experimental

All chemicals used for the synthesis were of reagent grade and procured from Sigma-Aldrich, Bangalore, India. ¹H and ¹³C NMR spectra were recorded on AS 400 MHz Varian

NMR spectrometer using TMS as an internal standard. IR spectra were recorded by using Perkin-Elmer Spectrum 100 Series FT-IR spectrometer. Mass spectra were recorded on Agilent 1200 Series LC/MSD VL system. All the reactions were monitored by thin layer chromatography (TLC) using precoated silica 60 F254, 0.25 mm aluminum plates (Merck). The crude compounds were purified by column chromatography using silica gel (100-200 mesh) and gradient (0 - 10%) ethyl acetate in hexane as the eluent system.

General procedure for the synthesis of cyclopentenone derivatives

To a solution of 1-acetyl -1-cyclohexen (**1**) (200 mg, 1.61 mmol) in acetic acid (2.0 mL) aromatic aldehyde (**2a-j**) was added at room temperature followed by conc. sulfuric acid (158 mg, 1.61 mmol). The resultant mixture was heated to 60-65 °C for 6-16 h. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (25 mL), washed with 10% sodium bicarbonate solution (2x20 mL). The organic phase was washed with water (20 mL) followed by saturated brine solution (20 mL), dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography (Silica gel 100-200 mesh, 0-10% ethyl acetate in hexane as eluent) to afford the title compound **3a-j** in 55 to 75% yield.

3-Phenyl-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3a)

Yield 62%, Pale yellow liquid, IR (KBr): 3309, 2931, 1697, 1392, 701 cm^{-1} ; MS (ESI): 213.1 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 7.33-7.22 (m, 3H), 7.08 (d, $J = 6.8$ Hz, 2H), 3.82 (m, 1H), 2.88 (dd, $J = 19.2, 7.2$ Hz, 1H), 2.39-2.04 (m, 5H), 1.62 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.3, 174.2, 140.8, 138.2, 127.8, 126.2, 125.9, 47.1, 43.9, 25.4, 21.1, 20.6, 19.1.

3-(4-Methylphenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3b)

Yield 54%, Pale yellow liquid, IR (KBr): 3377, 2924, 1700, 1389, 817 cm^{-1} ; MS (ESI): 227.1 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 7.11 (d, $J = 8.0$ Hz, 2H), 6.96 (d, $J = 8.0$ Hz, 2H), 3.79 (m, 1H), 2.85 (dd, $J = 18.8, 6.8$ Hz, 1H), 2.36-2.05 (m, 8H), 1.65 (m, 4H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.5, 174.5, 138.1, 137.8, 135.6, 128.5, 126.1, 46.6, 43.9, 25.4, 21.1, 20.6, 20.0, 19.1.

3-(4-Methoxyphenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3c)

Yield 58%, Pale yellow liquid, IR (KBr): 3380, 2928, 1698, 1247, 833 cm^{-1} ; MS (ESI): 243.1 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 6.99 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 3.79 (m, 4H), 2.84 (dd, $J = 18.8, 6.8$ Hz, 1H), 2.34-2.06 (m, 5H), 1.70-1.61 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 208.4, 175.5, 158.6, 139.0, 133.8, 128.2, 113.9, 55.3, 47.2, 45.1, 26.4, 22.1, 21.6, 20.1.

3-(4-Fluorophenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3d)

Yield 62%, Pale yellow liquid, IR (KBr): 3042, 2929, 1699, 1390, 837 cm^{-1} ; MS (ESI): 230.1 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 7.07-6.98 (m, 4H), 3.82 (m, 1H), 2.87 (dd, $J = 18.8, 7.2$ Hz, 1H), 2.33-1.98 (m, 5H), 1.66 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 174.8, 163.1, 160.5, 139.4, 137.5, 128.6, 116.1, 115.6, 47.2, 44.9, 26.3, 22.1, 21.5, 20.1.

3-(4-Chlorophenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3e)

Yield 70%, Off white solid, mp 102-104 °C; IR (KBr): 3352, 2931, 1702, 1367, 836 cm^{-1} ; MS (ESI): 246.9 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 7.29-7.26 (m, 2H), 7.01 (d, $J = 8.4$

Hz, 2H), 3.80 (m, 1H), 2.86 (dd, $J = 18.8, 7.2$ Hz, 1H), 2.32-1.97 (m, 5H), 1.65 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.8, 174.6, 140.4, 139.6, 132.7, 129.1, 128.6, 47.3, 44.7, 26.4, 22.1, 21.5, 20.1.

3-(4-Nitrophenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3f)

Yield 55%, Pale yellow semi solid, MS (ESI): 258 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 8.19 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 3.97 (m, 1H), 2.93 (dd, $J = 18.8, 7.2$ Hz, 1H), 2.36-2.1 (m, 5H), 1.68 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 206.1, 173.3, 149.6, 140.5, 128.2, 124.3, 47.7, 44.4, 26.5, 22.0, 21.4, 20.2.

3-(4-Bromo-2-fluorophenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3g)

Yield 60%, Pale brown semi solid, IR (KBr): 3068, 2928, 1701, 1483, 861 cm^{-1} ; MS (ESI): 309 $[\text{M}+2\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 7.27- 7.19 (m, 2H), 6.85 (t, 1H), 4.15 (m, 1H), 2.87 (dd, $J = 18.8, 7.2$ Hz, 1H), 2.34-2.02 (m, 5H), 1.73 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.3, 173.2, 161.9, 159.4, 140.0, 129.4, 127.9, 119.5, 119.2, 43.4, 40.1, 26.3, 22.1, 21.5, 20.1.

3-(3,4,5-Trimethoxyphenyl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3h)

Yield 74%, Off white solid; mp 88-90 $^\circ\text{C}$; IR (KBr): 3371, 2930, 1694, 1126, 843 cm^{-1} ; MS (ESI): 302.9 $[\text{M}+\text{H}]^+$; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 6.40 (s, 2H), 3.89 (m, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 2.76 (dd, $J = 18.4, 6.8$ Hz, 1H), 2.26-1.91 (m, 5H), 1.56 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 208.3, 175.3, 153.5, 139.3, 137.6, 136.8, 103.9, 60.8, 56.1, 48.3, 44.7, 26.5, 22.1, 21.6, 20.1.

3-(Thiophen-2-yl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one (3i)

Yield 58%, Pale yellow liquid, IR (KBr): 2942, 1695, 1256 cm^{-1} ; MS (ESI): 219 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 7.19- 7.17 (m, 1H), 6.95-6.93 (m, 1H), 6.84-6.83 (m, 1H), 4.16 (m, 1H), 2.91 (dd, $J = 18.8, 7.2$ Hz, 1H), 2.44 (dd, $J = 18.8, 2.4$ Hz, 1H), 2.23-2.10 (m, 4H), 1.63 (m, 4H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.1, 173.1, 145.3, 138.9, 126.9, 124.6, 124.1, 45.3, 42.9, 26.3, 22.6, 21.5, 20.1.

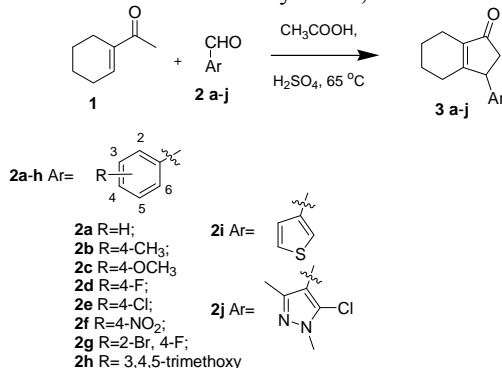
3-(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)-2,3,4,5,6,7-hexahydro-1H-inden-1-one(3j)

Yield 60%, Pale yellow liquid, IR (KBr): 2932, 1693, 1258 cm^{-1} ; MS (ESI): 267 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3 , 400 MHz): δ 3.82 (m, 1H), 3.75 (s, 3H), 2.79 (dd, $J = 18.8, 7.2$ Hz, 1H), 2.39-2.34 (m, 1H), 2.21 (s, 3H), 2.12 (m, 4H), 1.63 (m, 4H).

Results and Discussion

Cyclopentenones are generally synthesized by two steps; in step one, synthesis of divinyl ketone from enone and aldehyde; and in step two, cyclization to form cyclopentenone derivative by Lewis or Bronsted acid which is known as Nazarov cyclization. Synthesis of divinyl ketone from 1-acetyl-1-cyclohexene (**1**) with aldehydes (**2a-j**) was unsuccessful in both basic and acidic conditions. Basic conditions like NaOH, LDA yielded β -hydroxy ketone and in acidic conditions like ethanolic HCl, polyphosphoric acid, thionyl chloride the expected product did not form. However, when the reaction was carried out in acetic acid as solvent and a catalytic amount of sulfuric acid at 60-65 $^\circ\text{C}$ for 16 h, corresponding cyclopentenone derivative was obtained in one pot. Under the optimized condition a series of cyclopentenone derivatives (**3a-j**) were synthesized by condensation of various aldehydes

(**2a-j**) with 1-acetyl-1-cyclohexene (**1**) as depicted in Scheme 1. The reaction was carried out with various aldehydes containing electron donating and electron withdrawing groups. All the synthesized compounds were characterized by NMR, IR and mass spectral data.



Scheme 1. Synthesis of cyclopentenone derivatives (**3a-j**)

Biological evaluation

Antibacterial activity

The antimicrobial activity of synthesized compounds **3a-j** was carried out using agar well-diffusion method at Vidya Herbs Pvt. Ltd., Bangalore. The *in vitro* antimicrobial activity was carried out for 24 h culture against four bacterial strains Gram positive *Staphylococcus aureus*, *Bacillus subtilis*, Gram negative *Salmonella typhi* and *Escherichia coli*. The compounds were tested at 40 µg/mL concentration against bacterial strains. DMSO was used as a vehicle. Ciprofloxacin was used as standard drug for comparison of antibacterial activities. The zone of inhibition was compared with standard drug after 24 h of incubation at 37 °C for antibacterial activity. The results are recorded in Table 1. The MIC of all synthesized compounds **3a-j** was determined by a micro dilution method. The respective clinical strain was spread separately on the medium. The wells were created using a stainless steel sterilized cork borer under aseptic conditions. The synthesized compounds at different concentrations *viz.* 10, 20, 30, 40 and 50 µg was dissolved, respectively, in 25, 50, 75, 100 and 125 µL of DMSO and later loaded into corresponding wells, the results are given in Table 1 as minimum inhibitory concentration (MIC- µg/mL), Ciprofloxacin (40 µg in 100 µL) was used as standard drug.

Table 1. Antibacterial activity of **3a-j**

Compounds	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Salmonella typhi</i>	<i>Escherichia coli</i>
3a	R	25	R	12.5
3b	R	100	R	50
3c	25	50	25	25
3d	12.5	6.25	6.25	6.25
3e	6.25	12.5	12.5	25
3f	6.25	6.25	6.25	12.5
3g	12.5	12.5	6.25	12.5
3h	25	12.5	25	6.25
3i	12.5	12.5	12.5	25
3j	6.25	6.25	12.5	6.25

Activity expressed as MIC - µg/mL, Standard drug used: Ciprofloxacin, Quantity of compound used: 40 µg/mL, R = Resistance

Among the tested compounds, synthesized cyclopentenones **3e**, **3f** and **3j** showed excellent activity against *Staphylococcus aureus* bacterial strains with MIC 6.25 µg/mL. Compounds **3d**, **3f** and **3j** showed significant inhibition against *Bacillus subtilis* with MIC 6.25 µg/mL. The compounds **3d**, **3f** and **3g** showed excellent activity against *Salmonella typhi* and **3d**, **3h**, **3j** showed excellent activity against *Escherichia coli*. Compounds **3a** and **3b** are inactive against *Staphylococcus aureus*, *Bacillus subtilis* and *Salmonella typhi* bacterial stains. Compounds **3d** and **3i** showed excellent inhibition against all the bacterial strains tested. SAR study reveals that compounds having electron withdrawing groups like halogens, nitro on phenyl ring and substituted pyrazole have shown excellent activity.

Conclusion

A series of 10 novel cyclopentenone derivatives were synthesized and well characterized by their ¹H, ¹³C NMR, IR and mass spectral data. All the newly synthesized compounds were screened for their antibacterial activity. The antibacterial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested strains. Among the tested compounds **3d**, **3e**, **3f** and **3j** showed excellent activity against all the bacterial strains. Compounds having electron withdrawing groups on phenyl ring and substituted pyrazole showed excellent activity. Hence the fact that the compounds prepared in this study are chemically unrelated to the current medication, suggests that further work with similar analogs is clearly warranted.

Acknowledgement

This work was carried out as part of Mr. Manjunath Moger's Ph.D. work. Authors are grateful to Advinus Therapeutics Ltd, Bangalore, India, for their support and encouragement to higher education. Authors also thank the Department of Chemistry, Mangalore University, India.

References

1. Gao S, Wang Q and Chen C, *J Am Chem Soc.*, 2009, **131(4)**, 14100-14112; DOI:10.1021/ja808110d
2. Harrington P E and Tius M A, *J Am Chem Soc.*, 2001, **123(35)**, 8509-8514; DOI:10.1021/ja011242h
3. Motoyoshiya J, Mizuno K, Tsuda T and Hayashi S, *Syn lett.*, 1993, 237.
4. Varlet D, Depreux P, Lesieur I and Pfeiffer B, *Synth Commun.*, 1996, **26(23)**, 4319-4328; DOI:10.1080/00397919608003834
5. Johnson C R and Penning T D, *J Am Chem Soc.*, 1988, **110(14)**, 4726-4735; DOI:10.1021/ja00222a034
6. Usami Y and Numata A, *Synlett.*, 1999, **6**, 723
7. Malmstrom J, Christophersen C, Barero A F, Oltra J E, Justicia J and Rosales A, *J Nat Prod.*, 2002, **65(3)**, 364-367; DOI:10.1021/np0103214
8. Pettit G R, Singh S B, Hamel E, Lin C M, Alberts D S and Garcia-Kendall D, *Experientia*, 1989, **45(2)**, 209-211.
9. Nam N H, Kim Y, You Y J, Hong D H., Kim H M and Ahn B Z, *Bioorg Med Chem Lett.*, 2002, **12(15)**, 1955-1958; DOI:10.1016/S0960-894X(02)00321-9
10. Lee S, Kim W G, Kim E, Ryoo I J, Lee H K, Kim J N, Jung S H and Yoo I D, *Bioorg Med Chem Lett.*, 2005, **15(2)**, 471-473; DOI:10.1016/j.bmcl.2004.10.057
11. Moger M, Pradhan A K, Hindupur R M and Pati H.N, *Tetrahedron Lett.*, 2014, **55(16)**, 2675-2678; DOI:10.1016/j.tetlet.2014.03.038