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Synthesis, anti-inflammatory activity of picen-13-ylmethylene derivatives

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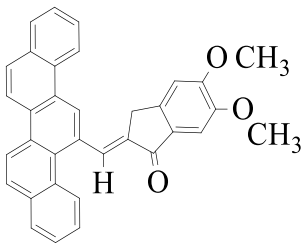
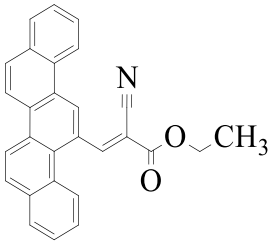
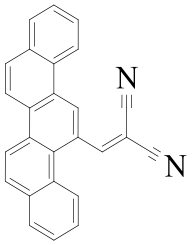
Abstract

A series of picene-13-ylmethylene derivatives **(11-17)** were synthesized by Knoevenagel condensation of active methylene compounds with picene-13-carbaldehyde.







Keywords: Photo cyclization, picene-13-carbaldehyde, picene-13-ylmethylene derivatives, anti-inflammatory

Introduction

Picene or benzo[*a*]chrysene, is well documented for use in material chemistry.[1,2] Picene derivatives were found to be present in abundance as pentacyclic triterpenes and triterpenoids which are often bioactive and present a huge therapeutic potential. Many pentacyclic triterpenes namely oleane, oleanolic acid and ursane are reported to possess promising antitumor,[3-5] antiviral,[6] antidiabetic,[7] anti-inflammatory[8] activities. Also a derivative of picene, namely octadecahydro-picene-2,3,14,15-tetranone isolated and purified from the root bark of Zizyphus nummularia, reported to possess anti-cancer and anti-inflammatory activities.[9,10]

Many polycyclic aromatic compounds such as flavone, quercetin, chrysin and pyrimido[4,5-b]quinolines were reported to possess anti-inflammatory or antioxidant properties.[11,12] Because of the close structural similarity with the reported polycyclic compounds, we have envisaged to explore the anti-inflammatory activity of picene analogues. Thus, our interest is to conjugate two naphthalene moieties by cyclization which results in the formation of a picene moiety. Substitution at its alpha position with various esters or amides leads to novel picene methylene derivatives in order to evaluate their biological properties. In order to accomplish our objective, we used a Knoevenagel condensation for the synthesis of novel structures incorporating both the picene moiety and several active methylene compounds, namely, ethyl cyanoacetate, malononitrile, cyanoacetamide, diethyl malonate, ethyl acetoacetate, acetylacetone and 5,6 dimethoxy-1-indanone with picene-13-carbaldehyde. The synthesized picen-13-ylmethylene derivatives were characterized by NMR, IR, mass spectra, elemental analysis. The structures were confirmed by single crystal XRD of a selected example. The compounds were evaluated by in vitro biological tests for their anti-inflammatory properties.

Results and Discussion

In the present work, we synthesized a new series of picen-13-ylmethylene derivatives **11-17** by condensing active methylene groups with picene-13-carbaldehyde as shown in Scheme 1 and 2. The first step in the Scheme 1 was the condensation of 1-naphthaldehyde **1** with 1-naphthyl acetic acid **2** in the presence of triethylamine and acetic anhydride produced 2,3-di(naphthalen-1-yl)acrylic acid **3**[13,14] with 62% yield after recrystallization from ethyl acetate.

Table 1. Reaction conditions and yield of **3** for the esterification using an alcohol

Solvent	Reaction condition	Reaction Time	Reaction conversion	Product Yield %
Ethanol	Reflux	3 days	60%	50% of compound **4**
Mixture of Ethanol and Toluene	Reflux	10 hrs	100%	86% of compound **4**
Methanol	Reflux	3 days	60%	50% of compound **5**
Mixture of Methanol and Toluene	Reflux	10 hrs	100%	87% of compound **5**

Compound **3** was then converted to the corresponding ester **4** & **5** using ethanol or methanol and a catalytic amount of sulphuric acid. Esterification of compound **3** with ethanol and sulphuric acid under reflux condition over 3 days gave 50% yield of compound **4**. As the starting compound **3** was insoluble in 25 volumes of ethanol under reflux condition, we conducted the experiment using toluene as solvent under Dean Stark conditions. Under continuous removal of water, the esterification reaction was completed in 10 hours with 91% yield of compound **4** without further purification. (Table 1)

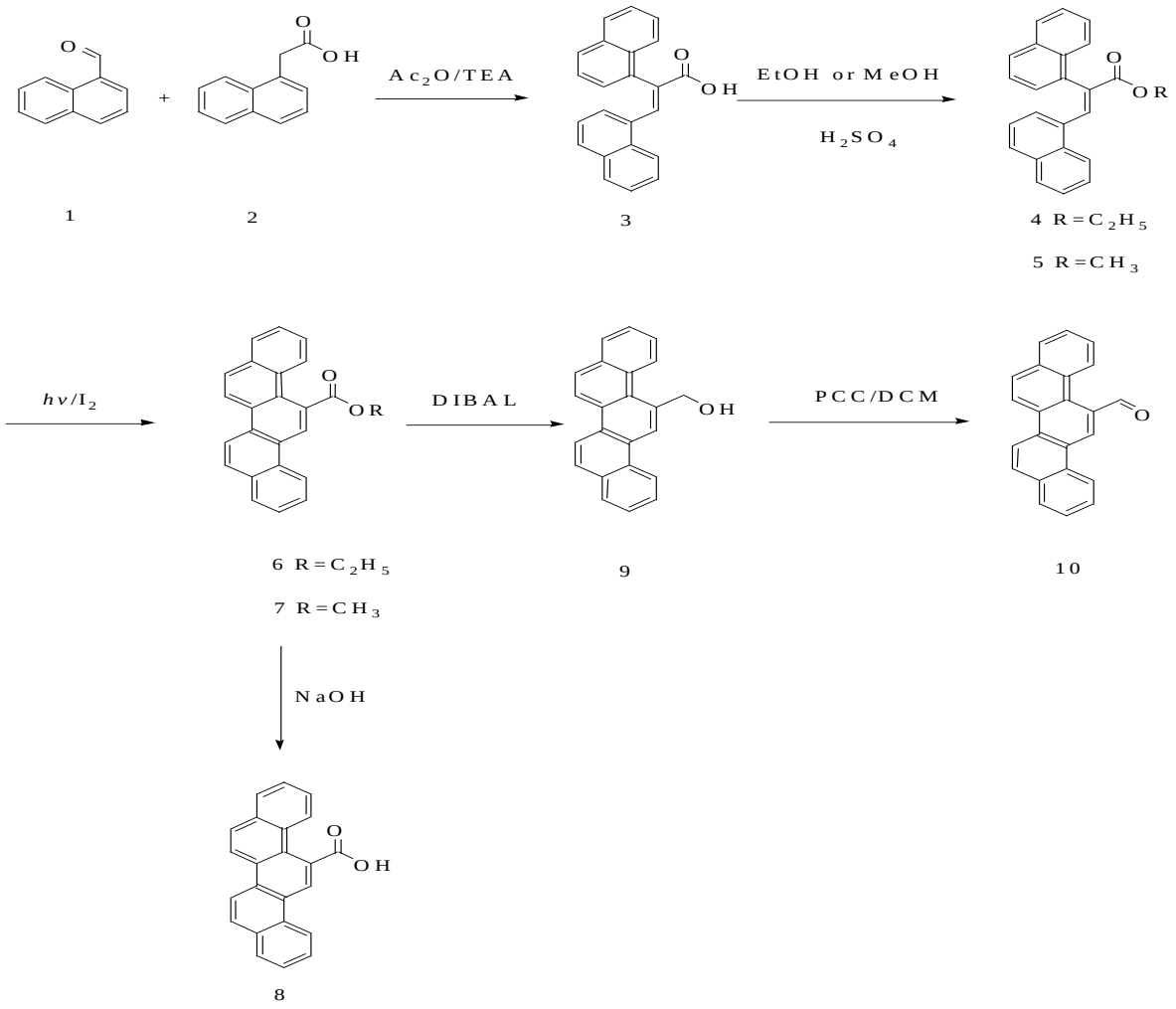
The ester was cyclized to ethyl or methyl picene-13-carboxylate **6** & **7**[15-19] under irradiation with UV light at 365 nm in the presence of iodine. We studied the oxidative cyclisation of compound **4** with several reactants under different reaction conditions and the results are summarized in Table 2. Treatment of compound **4** with aluminium chloride; or a mixture containing aluminium chloride and sodium chloride[20] at 140 °C; or aluminium chloride and stannic chloride[21] ;or irradiation with 254 nm in the presence of iodine gave no product. Irradiation of compound **4** with 365 nm light without stirring condition gave 30% yield. The previously reported process[22] of vanadium trifluoride oxide in trifluoroacetic acid afforded picene-13-carboxylic acid methyl ester **7** with a yield of 47%. In our present study, it was found that 1 mole of iodine and irradiation with light of 365nm in benzene under stirring are necessary to produce compound **6** & **7** in good yield (86% & 87% respectively) without chromatographic purification.

Table 2. Mole ratio of reactants, reaction conditions and yield for the oxidative cyclisation of Compound **4**

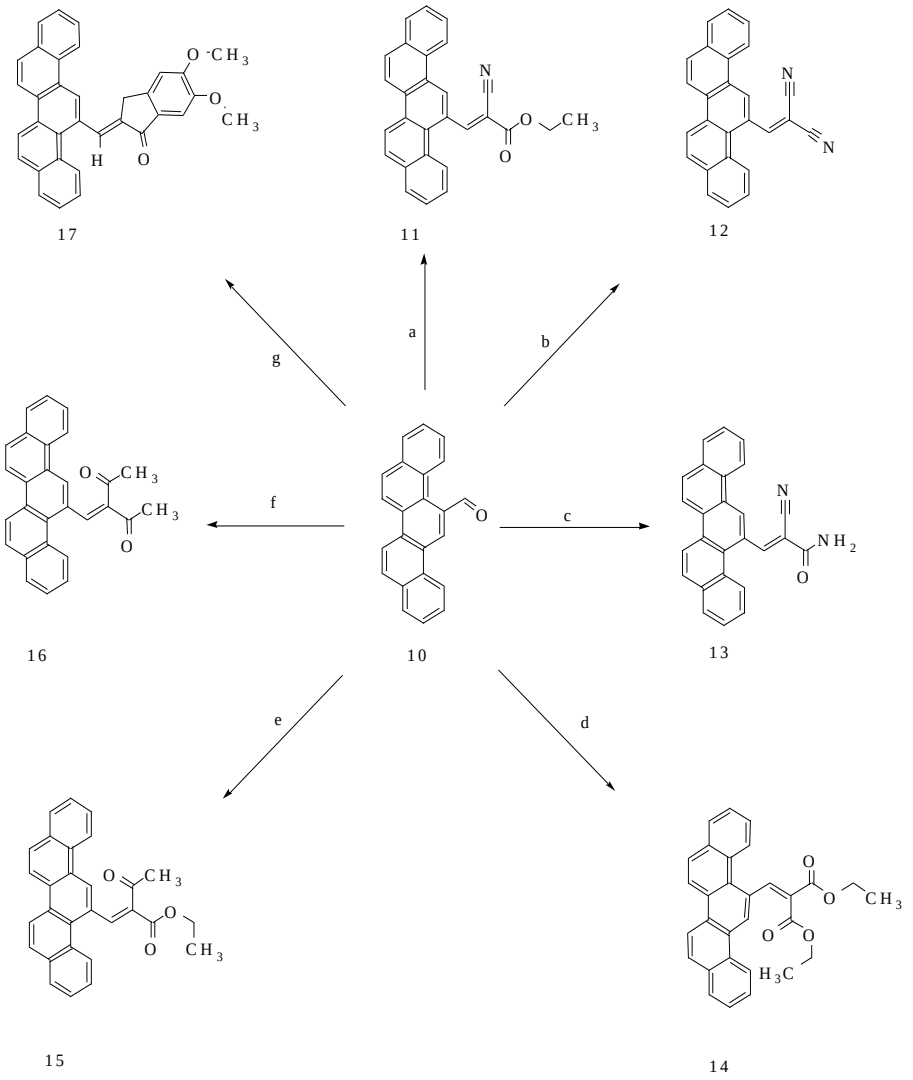
Reactant	Solvent	Temperature (°C)	Reaction time (hrs.)	Yield (%) of **6**
$AlCl_3$ (5 mol equiv) & Sodium Chloride (5 mol equiv)	Neat	140 °C	6	No product
$AlCl_3$ (5 mol equiv)	Benzene	Reflux	6	No product
$AlCl_3$ (5 mol equiv) & Stannic Chloride (2.5 mol equiv)	Benzene	Reflux	6	No product
Iodine (1mol equiv); irradiation at 254 nm	Benzene	25-30°C, without stirring	12	No product
Iodine (1mol equiv); irradiation at 254 nm	Benzene	25-30°C, with stirring	12	No product
Iodine (1mol equiv); irradiation at 365 nm	Benzene	25-30°C, without stirring	12	30
Iodine (1mol equiv); irradiation at 365 nm	Benzene	25-30 °C, with stirring	12	86[15-19]
Iodine (3mol equiv); irradiation at 500 nm	cyclohexane	Not reported	Not reported	31[22,15] (after column chromatography)
Vanadium Trifluoride oxide (4.4 mol equiv)	Dichloromethane	0 °C	Not reported	47[22]

The picene-13-carboxylic acid ethyl ester **6** was hydrolyzed with sodium hydroxide produced picene-13-carboxylic acid **8** in 88% yield.

Reduction of picene-13-carboxylic acid methyl ester with lithium aluminium hydride has been reported for the preparation of compound **9** with a yield of 97%.[23] In our study, mild reducing agents like di-isobutyl aluminium hydride [DIBAL (1M in Toluene)] was used to reduce picene-13-carboxylic acid ethyl ester **6** to picen-13-ylmethanol **9**[24] in 90% yield. It was found that the oxidation of compound **9** with manganese dioxide[11] in dichloromethane was not completed even under reflux condition. Therefore, we tried pyridinium chlorochromate as an oxidising agent in dichloromethane at 25-30 °C and obtained the compound **10**[25,26] in 87% yield without further purification. The picene-13-carbaldehyde **10** was condensed with active methylene compounds using piperidine as a base to give the title compounds **11-17**.[27,28]



Scheme 1. Synthetic route for Picene-13-carboxylic acid (**8**) and Picene-13-carbaldehyde (**10**).



Scheme 2. Synthetic route for various picen-13-ylmethylene derivatives (**11-17**) a) ethyl cyanoacetate b) malononitrile c) cyanoacetamide d) diethylmalonate e) ethyl acetoacetate f) acetyl acetone and g) 5,6 dimethoxy-1-indanone.

All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, Mass and elemental analysis. The structure of **11** was confirmed by single crystal X-ray diffractogram (CCDC No. CCDC 1400968). Based on the single crystal structure, the configuration of the compound was confirmed as the *E*-isomer. The crystal parameters for compound **11** are given in Table 3 and the ORTEP diagram is shown in Figure 1.

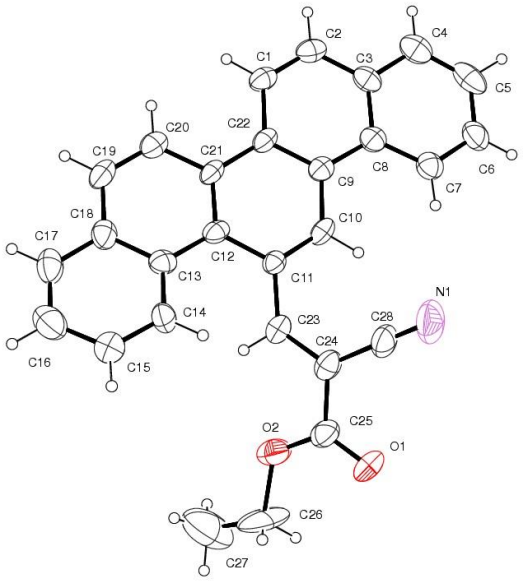


Figure 1. ORTEP diagram of Compound **11**.

Table 3. Crystal data and structure refinement for Compound **11**

Empirical formula	$C_{28}H_{19}NO_2$
Formula weight	402.1
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 11.4481(11) Å alpha = 108.889(3)° b = 12.8106(11) Å beta = 97.646(3)° c = 15.4300(13) Å gamma = 90.531(3)°
Volume	2118.7(3) $Å^3$
Z, Calculated density	2, 1.259 g/cm^3
Absorption coefficient	0.079 mm^{-1}
F(000)	840
Crystal size	0.210 x 0.150 x 0.100 mm
Theta range for data collection	1.409 to 21.57°
Limiting indices	-11<=h<=11, -13<=k<=13, -15<=l<=15
Reflections collected / unique	18796 / 4896 [R(int) = 0.0741]
Completeness to theta =	21.570 99.90%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4896 / 0 / 561
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0735, wR2 = 0.2161
R indices (all data)	R1 = 0.1930, wR2 = 0.3213
Extinction coefficient	n/a
Largest diff. peak and hole	0.391 and -0.181 $eÅ^{-3}$

Anti-inflammatory activity. The synthesized compounds were screened for *in vitro* anti-inflammatory activity using the inhibition of bovine serum albumin denaturation method. From the activity data, the anti-inflammatory activity screening revealed that compounds containing the active methylene groups such as diethylmalonate **14**, acetylacetone **16**, and 5,6 dimethoxy-1-indanone **17** attached to a picene-13-carbaldehyde moiety exhibited the biggest potent anti-inflammatory activity comparable to diclofenac sodium as a reference standard. In addition the data indicated that, the cyano ester **11** or cynamide **13**, malononitrile **12** and ethyl acetoacetate ester **15** of picene-13-ylmethylene are comparatively less potent than its malonate **14** or dione **16** or indanone **17** derivatives and moderate activity in comparison to diclofenac sodium (Table 4).

Table 4. *In vitro* anti-inflammatory activity of compounds **6-10** & **11-17** by inhibition of protein (Bovine serum albumin) denaturation method

Compound	Activity (% inhibition of protein denaturation)			
	50 µg /mL	100 µg /mL	400 µg /mL	800 µg /mL
6	15.81	27.02	35.91	50.88
7	14.82	25.26	32.55	48.88
8	10.59	26.72	45.64	62.41
9	14.02	22.51	35.86	48.86
10	14.28	24.85	47.21	52.34
11	17.97	29.81	38.82	55.69
12	16.61	29.42	37.88	54.65
13	13.21	27.11	32.95	53.21
14	30.32	50.15	70.32	84.48
15	11.09	21.89	32.24	49.13
16	27.81	49.62	64.99	80.38
17	27.88	38.93	66.12	78.65
Std	29.24	50.64	65.38	75.38

Std - Diclofenac sodium.

Conclusions

A new versatile method with improved yield for the photocyclisation of 2,3-di(naphthalen-1-yl)acrylic acid ester was reported using mild conditions i.e., UV irradiation. A new series of picene-13-ylmethylene derivatives were synthesized, characterized and evaluated for *in vitro* anti-inflammatory activity. Among the picene-13-ylmethylene derivatives, compounds **14**, **16** and **17** possess promising anti-inflammatory activity compared to the reference drug diclofenac sodium.

Experimental Section

General. All the chemicals and reagents used were lab grade material procured from Alfa aesar. The melting points were determined using Buchi apparatus by the open capillary tube method. The IR spectra were recorded in Perkin-Elmer series 2000 FTIR spectrophotometer using KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$, DMSO-d_6 on a Bruker spectrometer at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard, coupling constants (*J*) are in hertz (Hz). Mass were recorded on ESI – Perkin Elmer Sciex, API 3000 mass spectrometer. Pre-coated silica gel GF_{254} plates from Merck were used for thin layer chromatography. The elemental analyses were recorded in Thermo Finnigan Flash EA 1112 elemental analyser.

2,3-Di(naphthalen-1-yl)acrylic acid (3). A mixture of 1-naphthaldehyde **1** (0.1 mole), 1-naphthylacetic acid **2** (0.1 mole), triethylamine (10 mL) and acetic anhydride (20 mL) was heated at reflux over 15 hours. The reaction progress was monitored using TLC (hexane: ethyl acetate; 7:3). After completion, the reaction mixture was poured into 200 mL water and extracted with ethyl acetate (2 x 250 mL). The combined organic layer was washed with water and evaporated. The residue was triturated with 200 mL of ethyl acetate: heptane mixture in the ratio of 10: 90 produced 28 g of the 2,3-di(naphthalen-1-yl)acrylic acid which was recrystallized from ethyl acetate afforded the title compound (20 g, 62%) as a Pale yellow powder. mp 232-235 °C (lit.[13]: 227-228 °C & lit.[14]: 232-233 °C). IR (solid, KBr, vmax, cm^{-1}): 3435, 3054, 1674, 1506, 1423, 1275, 800, 777. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.85 (s, 1H), 8.26 (d, *J* 8.4 Hz, 1H), 7.91 (d, *J* 7.8 Hz, 1H), 7.83 (d, *J* 7.6 Hz, 1H), 7.78 (t, *J* 8.6 Hz, 2H), 7.60 (t, *J* 8.5 Hz, 2H), 7.51 (t, *J* 7.4 Hz, 1H), 7.46-7.39 (m, 2H), 7.31-7.27 (m, 1H), 7.20 (d, *J* 6.9 Hz, 1H), 6.93 (t, *J* 7.6 Hz, 1H), 6.81 (d, *J* 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO-d_6): δ_C 170.1, 140.2, 133.9, 133.8, 133.6, 133.3, 132.5, 132.0, 131.9, 129.1, 128.7, 128.5, 128.2, 127.8, 127.2, 126.6, 126.4, 126.0, 125.9, 125.6, 125.4, 125.1, 124.0. ESI-MS *m/z* calcd 324.1. Found: 325.0 $[M+H]^+$, 342.0 $[M+NH_4]^+$. Anal. calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97. Found: C, 85.12; H, 5.06.

Ethyl 2,3-di(naphthalen-1-yl)acrylate (4). 2,3-Di(naphthalen-1-yl)acrylic acid **3** (0.03 mole), ethanol (75 mL) and sulphuric acid (0.03 mole) was heated at reflux in toluene (50 mL) under a Dean-Stark water separator over 10 hours. The reaction was monitored using TLC (hexane: ethyl acetate; 7:3). After completion, the reaction mixture was evaporated under vacuum and the product was extracted with ethyl acetate (200 mL). The ethyl acetate layer was washed with water, aqueous sodium hydroxide solution, water and evaporated under vacuum. The residue was triturated with hexane (50 mL), filtered and dried at 50 °C under vacuum afforded the title compound (9.9 g, 91%) as a Off-white powder. mp 115-117 °C. IR (solid, KBr, vmax, cm^{-1}): 3433, 3055, 2974, 1705, 1626, 1504, 1271, 801, 774. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.79 (s, 1H), 8.25 (d, *J* 8.4 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.79 (t, *J* 8.9 Hz, 2H), 7.61-7.39 (m, 5H), 7.29 (t, *J* 7.1 Hz, 1H), 7.16-7.14 (m, 1H,), 6.94 (t, *J* 7.6 Hz, 1H), 6.79 (d, *J* 7.3 Hz, 1H), 4.32 (quartet, *J* 7.1 Hz, 2H), 1.22 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.1, 140.0, 134.0, 133.9, 133.6, 133.4, 132.7, 132.1, 131.9, 129.2, 128.8, 128.6, 128.3, 127.9, 127.4, 126.7, 126.4, 126.1, 125.9, 125.7, 125.4, 125.2, 124.1, 61.4, 14.4. ESI-MS *m/z* calcd 352.1. Found: 353.1 $[M+H]^+$. Anal. calcd for $C_{25}H_{20}O_2$: C, 85.20, H, 5.72. Found: C, 85.16; H 5.76.

Methyl 2,3-di(naphthalen-1-yl)acrylate (5). 2,3-Di(naphthalen-1-yl)acrylic acid (**3**) (0.012 mole), methanol (60 mL) and sulphuric acid (0.012 mole) was heated at reflux in toluene (40 mL) under a Dean-Stark water separator over 10 hours. The reaction was monitored using TLC (hexane: ethyl acetate; 7:3). After completion, the reaction mixture was evaporated under vacuum and the product was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with water, aqueous sodium hydroxide, water and evaporated under vacuum. The residue was triturated with hexane (20 mL), filtered and dried at 50 °C under vacuum afforded

the title compound (4.0 g, 96%) as a Pale yellow powder. mp 135-137 °C. IR (solid, KBr, vmax, cm^{-1}): 3401, 2045, 2941, 1709, 1628, 1505, 1425, 1275, 801, 763. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.82 (s, 1H), 8.25 (d, *J* 8.4 Hz, 1H), 7.86 (t, *J* 6.8 Hz, 2H), 7.80 (t, *J* 7.0 Hz, 2H), 7.62-7.58, (m, 2H), 7.53-7.41 (m, 3H), 7.31 (t, *J* 7.2 Hz, 1H), 7.18 (d, *J* 7.0 Hz, 1H), 6.94 (t, *J* 7.6 Hz, 1H), 6.79 (d, *J* 7.2 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.7, 140.4, 133.8, 133.7, 133.5, 133.4, 132.7, 132.2, 131.8, 129.3, 128.8, 128.7, 128.4, 127.9, 127.4, 126.8, 126.6, 126.2, 126.0, 125.7, 125.3, 125.2, 124.1, 52.7. ESI-MS *m/z* calcd 338.1. Found: 339.2 $[M+H]^+$, 356.2 $[M+NH_4]^+$. Anal. calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.16; H, 5.26.

Ethyl picene-13-carboxylate (6). A solution of compound **4** (0.006 mole) and iodine (0.006 mole) in benzene (25 mL) was stirred under irradiation with 365 nm light in a water cooled quartz immersion well for 12 hours. The completion of reaction was monitored using TLC (hexane: ethyl acetate 7:3). After completion, the reaction mass was washed with sodium sulphite solution, water and dried with anhydrous sodium sulfate. The solvent was evaporated and triturated with cyclohexane (5 mL), filtered and dried at 50 °C under vacuum afforded the title compound (1.8 g, 86%) as a Off-white powder. mp 172-174 °C. IR (solid, KBr, vmax, cm^{-1}): 3427, 2975, 1713, 1604, 1445, 1265, 808, 775. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.07 (s, 1H), 8.83 (d, *J* 8.3 Hz, 1H), 8.74 (d, *J* 9.2 Hz, 1H), 8.71 (d, *J* 9.3 Hz, 1H), 8.33 (d, *J* 8.0 Hz, 1H), 8.06 (t, *J* 8.8 Hz, 2H), 7.99 (d, *J* 8.1 Hz, 2H), 7.76 (t, *J* 8.1 Hz, 1H), 7.68-7.58 (m, 3H), 4.57 (quartet, *J* 7.1 Hz, 2H), 1.33 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.6, 132.9, 132.2, 130.6, 130.0, 129.9, 129.5, 129.4, 128.8, 128.7, 128.5, 127.6, 127.5, 127.2, 126.9, 126.1, 125.9, 124.2, 123.4, 121.5, 121.4, 62.2, 14.2; ESI-MS *m/z* calcd 350.1. Found: 351.2 $[M+H]^+$, 368.1 $[M+NH_4]^+$. Anal. calcd for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.72; H 5.10.

Methyl picene-13-carboxylate (7). A solution of compound **5** (0.003 mole) and iodine (0.003 mole) in benzene (25 mL) was stirred using magnetic stirrer under irradiation with 365 nm light in a water cooled quartz immersion well for 12 hours. The completion of reaction was monitored using TLC (hexane: ethyl acetate 7:3). The reaction mass was washed with sodium sulphite solution, water and dried with anhydrous sodium sulfate. The solvent was evaporated and triturated with cyclohexane (5 mL), afforded the title compound (0.85 g, 87%) as a Colorless powder. mp 227-230 °C. [lit.[22]: 230-233 °C]. IR (solid, KBr, vmax, cm^{-1}): 3416, 2945, 1799, 1604, 1435, 1264, 808, 765. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.09 (s, 1H), 8.84 (d, *J* 8.3 Hz, 1H), 8.77-8.72 (m, 2H), 8.27 (d, *J* 7.3 Hz, 1H), 8.10 (t, *J* 9.9 Hz, 2H), 8.02 (d, *J* 8.0 Hz, 2H), 7.78 (t, *J* 7.2 Hz, 1H), 7.68-7.62 (m, 3H), 4.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.0, 132.9, 132.2, 130.6, 130.0, 129.5, 129.4, 129.0, 128.8, 128.6, 127.5, 127.4, 127.3, 126.9, 126.8, 126.1, 124.3, 123.4, 121.5, 121.4, 52.9. ESI-MS *m/z* calcd 336.1. Found: 337.2 $[M+H]^+$, 354.2 $[M+NH_4]^+$. Anal. calcd for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79. Found: C, 85.56; H, 4.76.

Picene-13-carboxylic acid (8). A mixture of compound **6** (0.001 mole), tetrahydrofuran (8 mL), water (2 mL) and sodium hydroxide (0.001 mole) was heated to reflux over 8 hours. The completion of the reaction was checked using TLC (hexane: ethyl acetate 1:1). The mass was acidified with concentrated hydrochloric acid and the product was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with water and evaporated. The residual mass was triturated with cyclohexane (5 mL), filtered and dried at 50 °C under vacuum afforded the title compound (0.28 g, 88%) as a Pale brown powder. mp 267-270 °C. IR (solid, KBr, vmax, cm^{-1}): 3435, 3206, 1676, 1425, 1252, 806,776. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 13.71 (s, 1H), 9.13 (s, 1H), 9.04-8.97 (m, 3H), 8.62-8.59 (m, 1H), 8.24-8.21 (m, 2H), 8.18-8.15 (m, 2H), 7.84-7.76 (m, 2H), 7.74-7.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 172.9, 132.3, 131.7, 131.1, 129.7, 129.4, 129.2, 128.8, 128.7, 128.5, 127.8, 127.7, 127.5, 127.1, 126.9, 126.3, 126.2, 124.7, 123.6, 122.5, 122.4, 121.9, 121.7. ESI-MS *m/z* calcd 322.1. Found: 340.2 $[M+NH_4]^+$, 321.2 $[M-H]^-$. Anal. calcd for $C_{23}H_{14}O_2$: C, 85.70; H, 4.38. Found: C, 85.74; H, 4.36.

Picen-13-ylmethanol (9). A solution of di-isobutyl aluminium hydride (1M in toluene 20%, 30 mL) was added slowly to a solution of compound **6** (0.007 mole) in dichloromethane (50 mL) at -75 °C under nitrogen

atmosphere over 30 minutes. The progress of the reaction was monitored by TLC. (hexane: ethyl acetate 7:3). After completion, the mass was quenched with methanol (10 mL) followed by the addition of 1:1 aqueous hydrochloric acid (20 mL) at -70 °C. The product was extracted with ethyl acetate (100 mL) and washed with water. The solvent was evaporated and triturated with toluene (40 mL), filtered and dried at 50 °C under vacuum afforded the title compound (1.94 g, 90%) as a Colorless powder. mp 192-195 °C. [lit.[23] 189.4 °C]. IR (solid, KBr, vmax, cm^{-1}): 3689, 3307, 3049, 2912, 1606, 1445, 1261, 1020, 977, 887, 803 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.23 (s, 1H), 9.09 (d, *J* 8.1 Hz, 1H), 9.00-8.94 (m, 3H), 8.15-8.12 (m, 4H), 7.84-7.74 (m, 4H), 5.96 (t, *J* 5.2 Hz, 1H), 5.38 (d, *J* 5.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 137.3, 132.6, 131.6, 129.9, 129.6, 129.5, 128.6, 128.4, 128.3, 128.2, 127.7, 127.5, 127.4, 127.3, 127.1, 126.9, 126.4, 126.2, 124.2, 123.2, 122.2, 121.9, 65.0. ESI-MS *m/z* calcd 308.1. Found: 367.1 $[M+CH_3COO]^-$. Anal. calcd for $C_{23}H_{16}O$: C, 89.58; H, 5.23. Found: C, 89.46; H, 5.36.

Picene-13-carbaldehyde (10). A suspension of compound **9** (1 g, 0.003 mole) in dichloromethane (60 mL) was added portionwise to a stirred mixture of pyridinium chlorochromate (1.04 g, 0.005mole) in dichloromethane (20 mL) at 25-30 °C. The reaction was monitored using TLC (hexane: ethyl acetate 7:3). The mass was filtered through celite and the filtrate was washed with water, aqueous sodium bicarbonate followed by water. The dichloromethane was evaporated and triturated with ethyl acetate (20 mL), filtered and dried at 50 °C under vacuum afforded the title compound (0.86 g, 87%) as a Pale brown powder. mp 181-184 °C. IR (solid, KBr, vmax, cm^{-1}): 3435, 3053, 2923, 1678, 1604, 1377, 1262, 799, 773 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.75 (s, 1H), 9.39 (s, 1H), 8.94 (d, *J* 8.2 Hz, 1H), 8.80-8.73 (m, 2H), 8.75 (d, *J* 9.1 Hz, 1H), 8.18-8.10 (m, 4H), 8.03 (d, *J* 7.8 Hz, 1H), 7.92-7.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 193.3, 133.1, 133.0, 132.0, 131.1, 130.4, 130.0, 129.3, 128.7, 128.6, 128.5, 127.9, 127.7, 127.6, 127.4, 127.3, 126.7, 124.6, 123.6, 121.6, 121.2. ESI-MS *m/z* calcd 306.1. Found: 307.2 $[M+H]^+$. Anal. calcd for $C_{23}H_{14}O$: C, 90.17; H, 4.61. Found: C, 90.16; H, 4.58.

General procedure for the synthesis of Picen-13-ylmethylene derivatives (11-17).

A mixture of compound **10** (0.001 mole), active methylene compound scheme 2 (**a-h**) (0.001 mole) in ethanol (5 mL) was heated under reflux for 3 hours using piperidine (0.5 mL) as a catalyst. The progress of the reaction was monitored using TLC (hexane: ethyl acetate 7:3). The reaction mass was cooled to 25-30 °C and the product was collected by filtration and recrystallized from ethanol afforded compounds **11-17**.

(*E*)-Ethyl 2-cyano-3-(picen-13-yl) acrylate (11). Prepared from **10** and ethyl cyanoacetate. Yellow powder, Yield: 80%. mp 199-201 °C. IR (solid, KBr, vmax, cm^{-1}): 3431, 3053, 2975, 2228, 1718, 1593, 1264, 1095, 803 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.53 (s, 1H), 9.12 (s, 1H), 9.08 (d, *J* 9.3 Hz, 1H), 9.03 (t, *J* 9.0 Hz, 2H), 8.41 (d, *J* 9.0 Hz, 1H), 8.31-8.28 (m, 2H), 8.25-8.24 (m, 1H), 8.20 (d, *J* 7.4 Hz, 1H), 7.90 (t, *J* 7.0 Hz, 1H), 7.83-7.78 (m, 3H), 4.49 (quartet, *J* 7.1 Hz, 2H), 1.43 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 162.7, 159.5, 133.3, 132.0, 130.7, 130.6, 130.3, 130.0, 129.9, 128.7, 128.6, 128.4, 128.0, 127.7, 127.6, 127.4, 127.1, 126.8, 125.6, 123.5, 121.6, 121.1, 103.0, 62.8, 14.3. ESI-MS *m/z* calcd 401.1. Found: 402.1 $[M+H]^+$, 419.1 $[M+NH_4]^+$. Anal. calcd for $C_{28}H_{19}NO_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.68; H, 4.68; N, 3.42.

2-(Picen-13-ylmethylene) malononitrile (12). Prepared from **10** and malononitrile. Orange powder, Yield: 90%. mp 258-260 °C. IR (solid, KBr, vmax, cm^{-1}): 3437, 3048, 2226, 1561, 1382, 798. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.54 (s, 1H), 9.34 (s, 1H), 9.04-8.98 (m, 3H), 8.42 (d, *J* 7.6 Hz, 1H), 8.28-8.24 (m, 2H), 8.22-8.17 (m, 2H), 7.87-7.79 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 165.4, 132.9, 131.7, 130.4, 130.2, 129.9, 129.6, 129.3, 129.1, 128.8, 128.6, 128.2, 128.0, 127.7, 127.5, 127.4, 126.9, 126.6, 126.0, 123.5, 121.9, 121.7, 114.4, 113.8, 84.9. ESI-MS *m/z* calcd 354.1. Found: 353.0 $[M-H]^-$. Anal. calcd for $C_{26}H_{14}N_2$: C, 88.11; H, 3.98; N, 7.90. Found: C, 88.10; H, 3.92; N, 7.88.

2-Cyano-3-(picen-13-yl)acrylamide (13). Prepared from **10** and cyanoacetamide. Yellow powder, Yield: 82%. mp 325-328 °C. IR (solid, KBr, vmax, cm^{-1}): 3401, 3155, 2221, 1693, 1586, 1394, 800. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.43 (s, 1H), 9.04-8.99 (m, 4H), 8.43 (s, 1H), 8.27-8.24 (m, 3H), 8.18-8.12 (m, 2H), 7.97 (s, 1H), 7.87 (m, 1H), 7.80 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 163.1, 155.6, 133.3, 132.2, 130.3, 130.1, 129.9, 129.8, 129.6, 129.3, 129.2, 129.1, 128.3, 128.1, 127.9, 127.7, 127.5, 127.4, 125.6, 123.8, 122.6, 122.2, 117.3, 109.5. ESI-MS *m/z* calcd 372.1. Found: 390.1 $[M+NH_4]^+$. Anal. calcd for $C_{26}H_{16}N_2O$: C, 83.85; H, 4.33; N, 7.52. Found: C, 83.78; H, 4.28; N, 7.48.

Diethyl 2-(picen-13-ylmethylene) malonate (14). Prepared from **10** and diethylmalonate. Pale yellow powder. Yield 75%. mp 135-138 °C. IR (solid, KBr, vmax, cm^{-1}): 3430, 3053, 2979, 1720, 1626, 1446, 1072, 807, 780. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.98 (s, 1H), 8.81-8.68 (m, 4H), 8.65 (s, 1H), 8.10-8.00 (m, 4H), 7.78-7.67 (m, 4H), 4.48 (quartet, *J* 7.1 Hz, 2H), 4.26 (quartet, *J* 7.1 Hz, 2H), 1.45 (t, *J* 7.1 Hz, 3H), 1.04 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 164.5, 148.4, 133.2, 132.1, 130.8, 130.6, 130.0, 129.4, 129.1, 128.6, 128.2, 127.9, 127.8, 127.7, 127.4, 127.1, 126.9, 126.8, 126.6, 126.2, 124.5, 123.4, 121.8, 121.5, 61.9, 13.9. ESI-MS *m/z* calcd 448.16. Found: 449.3$[M+H]^+$, 466.4 $[M+NH_4]^+$. Anal. calcd for $C_{30}H_{24}O_4$: C, 80.34; H, 5.39. Found: C, 80.28; H, 5.28.

Ethyl 3-oxo-2-(picen-13-ylmethylene)butanoate (15). Prepared from **10** and ethyl acetoacetate. Colourless powder, Yield: 75%. mp 178-180 °C. IR (solid, KBr, vmax, cm^{-1}): 3435, 3052, 2981, 1727, 1663, 1424, 1377, 1237, 1049, 807, 778. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.05-8.98 (m, 2H), 8.90 (s, 1H), 8.69-8.68 (m, 3H), 8.26-8.22 (m, 3H), 8.16 (m, 1H), 7.86-7.83 (m, 2H), 7.81-7.77 (m, 2H), 4.12 (quartet, *J* 7.0 Hz, 2H), 2.51 (s, 3H), 0.91 (t, *J* 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 195.8, 167.1, 147.2, 134.8, 132.8, 131.7, 130.7, 129.9, 129.6, 129.5, 129.1, 128.8, 128.7, 128.6, 127.8, 127.5, 127.2, 127.1, 126.8, 123.4, 122.6, 122.1, 121.8, 61.1, 26.9, 13.6. ESI-MS *m/z* calcd 418.15. Found: 419.3 $[M+H]^+$. Anal. calcd for $C_{29}H_{22}O_3$: C, 83.23; H, 5.30. Found: C, 83.38; H, 5.26.

3-(Picen-13-ylmethylene) pentane-2,4-dione (16). Prepared from **10** and acetylacetone. Brown powder, Yield: 70%. mp 185-188°C. IR (solid, KBr, vmax, cm^{-1}): 3435, 3051, 2920, 2850, 1706, 1655, 1377, 1236, 809, 778. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 9.04 (d, *J* 9.3 Hz, 1H), 8.98 (d, *J* 9.2 Hz, 1H), 8.83 (d, *J* 8.3 Hz, 1H), 8.77 (s, 1H), 8.71 (d, *J* 8.2 Hz, 1H), 8.59 (s, 1H), 8.27-8.20 (m, 2H), 8.17-8.15 (m, 2H), 7.87-7.81 (m, 2H), 7.79-7.75 (m, 2H), 2.62 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 204.9, 197.7, 145.9, 142.5, 133.3, 132.2, 131.2, 130.5, 130.1, 129.9, 129.5, 129.2, 129.1, 128.2, 128.0, 127.9, 127.6, 127.4, 127.2, 124.8, 123.2, 122.5, 122.2, 32.1 27.7. ESI-MS *m/z* Calcd 388.1; found: 389.3 $[M+H]^+$. Anal. calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.48; H, 5.25.

5,6-Dimethoxy-2-(picen-13-ylmethylene)-2,3-dihydro-1H-inden-1-one (17). Prepared from **10** and 5,6 dimethoxy-1-indanone. Yellow powder, Yield: 85%. m.p. 292-294 °C. IR (solid, KBr, vmax, cm^{-1}): 3435, 3051, 1684, 1499, 1304, 1129, 1096, 804. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ_H 9.05 (s, 1H), 8.82 (d, *J* 9.2 Hz, 2H), 8.77-8.74 (m, 2H) 8.46 (s, 1H), 8.09-8.06 (m, 2H), 8.04-8.02 (m, 2H), 7.79-7.75 (m, 1H), 7.72-7.69 (m, 1H), 7.68-7.65 (m, 1H), 7.64-7.58 (m, 1H), 7.45 (s, 1H), 7.05 (s, 1H), 4.14 (s, 2H), 4.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ_C 192.7, 155.5, 149.7, 145.6, 136.9, 135.3, 132.9, 132.1, 131.9, 131.5, 130.6, 130.2, 129.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.2, 127.0, 126.6, 126.3, 124.1, 122.9, 121.6, 121.5, 107.6, 105.1, 56.3, 56.1, 31.32, 29.6. ESI-MS *m/z* calcd 480.17. Found: 481.4 $[M+H]^+$. Anal. calcd for $C_{34}H_{24}O_3$: C, 84.98; H, 5.03. Found: C, 84.88; H, 5.18.

In vitro anti-inflammatory activity . The *in vitro* anti-inflammatory activity of synthesized compounds was studied using bovine serum albumin denaturation method.[29,30] In brief, increasing concentrations of the test or reference compound were incubated with 0.5% w/v of bovine serum albumin at 37 °C for 20 minutes and

the temperature was increased to keep the samples at 57 °C for 30 minutes. After cooling to room temperature, the turbidity was measured using UV-Visible spectrophotometer at 660 nm following addition of phosphate buffered saline. The control represents 100% protein denaturation. The results were compared with reference drug Diclofenac sodium. The percentage inhibition of protein denaturation by the drug was calculated by using the following formula.

Percentage Inhibition = 100-[(optical density of test solution-optical density of product control) ÷ (optical density of test control)] x 100

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