A Novel Procedure to Synthesize 3-Chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl Azetidin-2-ones and Exploration of Their Anti-Inflammatory Activity

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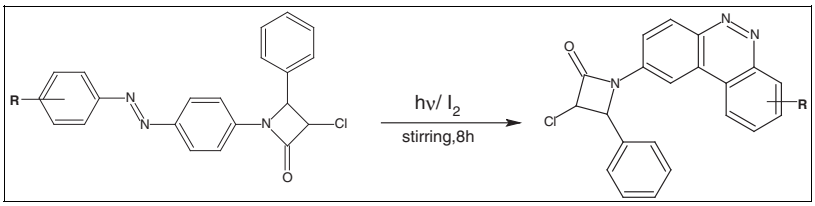

Some new derivatives of 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one were synthesized through the reaction of *N*-{4-[phenyldiazenyl] phenyl}-*N*-[phenyl methylene] amine with 4-[phenyldiazenyl] aniline. The resulting 3-chloro-4-phenyl-1-{4-[phenyldiazenyl] phenyl} azetidin-2-one intermediate in benzene was irradiated in a Pyrex vessel with 350 nm UV light in a photochemical reactor to give the desired derivatives **(4a–j)**. Structures of the new compounds were verified on the basis of spectral and elemental methods of analyses. Nine of the prepared compounds were tested for their anti-inflammatory effects; most of these compounds showed potent and significant results compared with indomethacin.

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INTRODUCTION

A number of polycyclic aromatic hydrocarbons (PAHs), including some nitrogen-heterocyclic analogs and aza-derivatives, have been shown to be carcinogenic to some extent in animals [1]. However, to greater extent PAHs together with corresponding polycyclic aza-aromatic compounds are of immense importance in astrophysics and life sciences [2–4]. Isolation of polycyclic aza-aromatic compounds from natural/environmental sources is very difficult, and hence, under these conditions biochemical studies has to rely on synthetic materials. A great deal of interest in the chemistry of these substances and their interaction with biomolecules is a subject of intense research now-a-days. The development of efficient and mild methods of synthesis of heterocyclic compounds represents a thrust area of intense research and development of these compounds [5–10]. In this context, nitrogen-containing heterocycles are among the most useful and widely demonstrated categories [11–16].

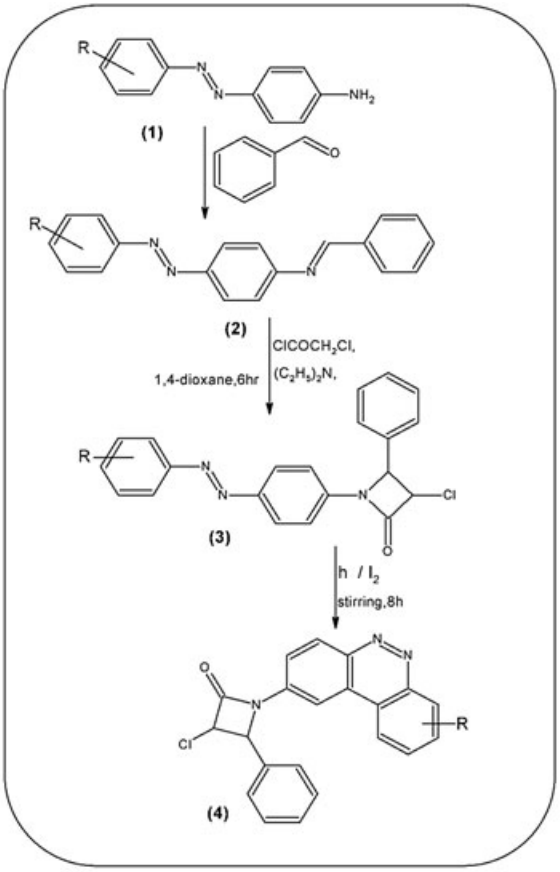
Despite the great biological potential residing in these compounds, little progress has been made in deducing antimicrobial behavior of polyaromatic hydrocarbons, which need to be investigated very thoroughly. Further, it has been observed that potency of several bacteria against commercially available drugs increases tremendously. As a result, there is an urgent need for new antibiotic agents, which can fight against bacterial infections. These threats have rekindled our interest in search of new compounds as potential antimicrobial agents. Thus in continuation of our previous work on heterocyclic systems [17–21], we herein report a short novel strategy to synthesize a number of 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one derivatives to be followed by an exploration of their anti-inflammatory potential using rat *carrageenan-induced paw edema* tests.

Inflammation is considered as a primary physiologic defense mechanism that helps body to protect itself against infection, burn, toxic chemicals, allergens, or other noxious stimuli. An uncontrolled and persistent inflammation may act as an etiologic factor for many of these chronic illnesses [22]. Although it is a defense mechanism, the complex events and mediators involved the inflammatory reaction can induce, maintain, or aggravate many diseases [23]. Currently used anti-inflammatory drugs are associated with some severe side effects. Therefore, the development of potent anti-inflammatory drugs with fewer side effects is necessary.

RESULTS AND DISCUSSION

Chemistry. The derivatives of 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one [stage D, compound **4a–j**] were synthesized through the reaction of *N*-{4-[phenyldiazenyl]phenyl}-*N*-[phenyl methylene] amine [stage B, compound **2**] with 4-[phenyldiazenyl] aniline [stage A, compound **1**]. The resulting 3-chloro-4-phenyl-1-{4-[phenyldiazenyl] phenyl}azetidin-2-one [stage-C, compound **3**] intermediate was irradiated in a Pyrex vessel with 350 nm UV light in a photochemical reactor in presence of benzene to give the desired derivatives

Scheme 1. An overview of synthetic schemes for 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one.



R	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j
	H	3-Cl	4-Cl	3-OH	3-C_2H_5	4-C_2H_5	4-NO_2	3-CH_3	4-CH_3	3-OCH_3

[**4a–j**]. This method involves exposure of cis/trans 3-chloro-4-phenyl-1-{4-[phenyldiazenyl] phenyl}azetidin-2-one [stage C, compound **3**] to UV light, which causes its isomerization to the cis-form. This form undergoes electrocyclic ring closure to produce phenanthrenes, which on dehydrogenation generates an azaphenanthrene derivatives [**4a–j**] (Scheme 1).

CONCLUSION

The results for compounds (**4a–j**) are presented in Table 2, which revealed that within a 3-h interval most of the test compounds exhibited anti-inflammatory activity comparable with that of indomethacin. On the other hand, only compounds **4e**, **4f**, and **4g** exhibited almost comparable results to those of indomethacin 5 h after injecting them, whereas compounds **4i** and **4j** showed only 85 and 85.9% of the activity of indomethacin.

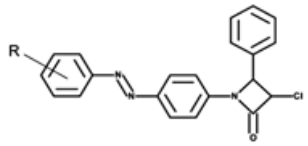
EXPERIMENTAL

Material and methods. All the chemicals used were of analytical grade purity. Melting points were taken in open capillary tubes using an electric melting point apparatus. All the melting points reported are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz with a Bruker advance DRX 300 instrument using TMS as an internal stranded. IR spectra were run on a Perkin-Elmer model 377-spectrophotometer using KBr pellets. Analytical thin layer chromatography was performed using E. Merck Silica gel-G 0.50-mm plates (Merck No. 5700).

Synthesis of 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one. ***Stage A: Synthesis of 4-[phenyldiazenyl] aniline {1}.*** An appropriate quantity of diazoaminobenzene (2.5 mL, 0.012*M*) and a pertinent aniline derivative (0.01*M*) was taken in a 100-mL flask and 1.3-g freshly prepared aniline hydrochloride was added into it and allowed to undergo heating at 40–45°C for 1 h on water bath with constant stirring. The reaction mixture was then permitted to stand for 15 min at room temperature. Now, 15.0-mL glacial acetic acid (1:1 V/V) was added to the contents and shaken thoroughly to remove excess aniline as aniline acetate. After

Table 1

Characterization and spectral data of 3-chloro-4-phenyl-1-{4-[phenyldiazenyl]phenyl} azetidin-2-one {3}.



S. No.	R[a]	MP (°C)[b]	Yield (%)	Elemental analysis found (calcd.) (%) C	H	N	IR (υ, cm[1])	^{1}H NMR (δ, ppm)
1	H	138–39	82	69.55 (69.71)	4.22 (4.46)	11.44 (11.61)	3080 (C—H, sp^2), 2010 (N=N), 1765 (C=O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 525 (C—Cl)	6.1 (s, CH, four-membered ring), 7.1 (s, 10H, $C_6H_5 \times 2$), 7.4–7.6 (d, 4H, Ar-H)
2	3-Cl	126–27	77	63.45 (63.65)	3.63 (3.82)	10.42 (10.60)	3072 (C—H, sp^2), 2019 (N=N), 1760 (C=O, four-membered), 1600, 1515, 1390 (C⋯⋯C, ring stretching), 812, 740 (subphenyl), 528 (C—Cl)	5.16 (s, CH, four-membered ring), 7.12–7.93 (s, 10H, $C_6H_5 \times 2$), 7.4–7.6 (d, 4H, Ar-H)
3	4-Cl	128–29	86	63.41 (63.65)	3.61 (3.82)	10.41 (10.60)	3083 (C—H, sp^2), 2012 (N=N), 1768 (C=O, four-membered), 1608, 1505, 1392 (C⋯⋯C, ring stretching), 819, 750 (subphenyl), 520 (C—Cl)	5.44 (s, CH, four-membered ring), 7.08–7.94 (s, 10H, $C_6H_5 \times 2$), 7.0–7.6 (d, 4H, Ar-H)
4	3-OH	131–32	84	66.52 (66.76)	4.11 (4.27)	11.08 (11.12)	3075 (C—H, sp^2), 2005 (N=N), 1770 (C=O, four-membered), 1610, 1500, 1402 (C⋯⋯C, ring stretching), 850, 765 (subphenyl), 580 (C—Cl)	5.16 (s, CH, four-membered ring), 6.93–7.40 (s, 10H, $C_6H_5 \times 2$), 7.30–7.96 (d, 4H, Ar-H), 5.0 (bs, OH)
5	3-C_2H_5	125–26	81	70.65 (70.85)	4.99 (5.17)	10.54 (10.78)	3070 (C—H, sp^2), 2025 (N=N), 1760 (C=O, four-membered), 1602, 1500, 1390 (C⋯⋯C, ring stretching), 840, 775 (subphenyl), 598 (C—Cl)	5.18 (s, CH, four-membered ring), 7.08–7.79 (s, 10H, $C_6H_5 \times 2$), 7.2–7.8 (d, 4H, Ar-H), 2.59 (t, 3H, CH_3), 1.24 (q, 2H, CH_2)
6	4-C_2H_5	136–37	78	70.64 (70.85)	5.01 (5.17)	10.52 (10.78)	3070 (C—H, sp^2), 2025 (N=N), 1760 (C=O, four-membered), 1602, 1500, 1390 (C⋯⋯C, ring stretching), 840, 775 (subphenyl), 598 (C—Cl)	5.18 (s, CH, four-membered ring), 7.08–7.79 (s, 10H, $C_6H_5 \times 2$), 7.2–7.8 (d, 4H, Ar-H),2.59 (t, 3H, CH_3), 1.24 (q, 2H, CH_2)
7	4-NO_2	135–36	81	(61.92) (62.00)	3.56 (3.73)	13.58 (13.78)	3050 (C—H, sp^2), 2015 (N=N), 1763 (C=O, four-membered), 1610, 1525, 1415 (C⋯⋯C, ring stretching), 1335 (NO_2)820, 745 (subphenyl), 520 (C—Cl)	5.10 (s, CH, four-membered ring), 7.12–8.86 (s, 10H, $C_6H_5 \times 2$), 7.4–7.6 (d, 4H, Ar-H)
8	3-CH_3	134–35	83	(70.15) (70.30)	4.65 (4.83)	11.02 (11.18)	3050 (C—H, sp^2), 2010 (N=N), 1765 (C=O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 575 (C—Cl)	6.1 (s, CH, four-membered ring), 7.1 (s, 10H, $C_6H_5 \times 2$), 7.4–7.6 (d, 4H, Ar-H) 2.35 (t, 3H, CH_3)
9	4-CH_3	130–31	78	70.12 (70.30)	4.60 (4.83)	11.01 (11.18)	3050 (C—H, sp^2), 2010 (N=N), 1765 (C=O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 575 (C—Cl)	5.35 (s, CH, four-membered ring), 7.1 (s, 10H, $C_6H_5 \times 2$), 7.4–7.6 (d, 4H, Ar-H), 2.35 (t, 3H, CH_3)
10	3-OCH_3	132–33	80	67.22 (67.43)	4.45 (4.63)	10.56 (10.72)	3080 (C—H, sp^2), 2010 (N=N), 1765 (C=O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 525 (C—Cl)	5.2 (s, CH, four-membered ring), 7.1 (s, 10H, $C_6H_5 \times 2$), 7.4–7.6 (d, 4H, Ar-H), 3.73 (t,O-CH_3)

[a]Substituent numbering is given as per their corresponding position in pertinent aniline.
[b]All the reported melting points are uncorrected.

Table 2

Inhibitory effects of test compounds upon carrageenan induced paw edema in rats.

	Edema inhibition (%)				
	Time after compound injection (h)				
Compound	0	1	2	3	5
5% gum acacia	–	–	–	–	–
Indomethacin[a]	7.16	23.50	43.32	66.16	92.25
4b[a]	1.72	13.50	35.51	38.34	46.00
4c[a]	1.97	6.25	35.76	63.65	43.00
4d[a]	0.24	16.75	50.12	60.40	34.00
4e[a]	0.98	13.50	48.11	63.40	90.80
4f[a]	0.24	18.00	37.53	62.90	90.50
4g[a]	1.23	12.75	39.79	56.39	56.50
4h[a]	2.22	18.75	43.32	63.65	91.25
4i[a]	1.72	9.75	38.43	63.50	78.50
4j[a]	0.74	11.75	37.53	61.65	79.25

[a]10 mg kg^{-1} body mass.

allowing the mixture to stand as such for 15-min yellow crystals of 4-(diphenyldiazene)aniline were obtained.

Stage B: Synthesis of N-{4-[phenyldiazenyl] phenyl}-N-[phenyl methylene] amine {2}. An appropriate quantity of 4-[phenyldiazenyl] aniline **{1}** (4.14 g, 0.02*M*) and benzaldehyde (2.12 mL) was taken in a 100-mL flask. To this, 3.0-mL glacial acidic acid in 25 mL of water was added and allowed to stand for 30 min with occasional shaking. The reaction mixture was then permitted to stand for 15 min at room temperature. Yellow crystals of *N*-{4-[phenyldiazenyl]phenyl}-*N*-[phenylmethylene] amine were obtained, filtered on Buchner funnel, and dried in vacuum.

Stage C: Synthesis of 3-chloro-4-phenyl-1-{4-[phenyldiazenyl] phenyl}azetidin-2-one{3}. To a constantly stirred solution of 1,4-dioxane (50 mL), chloroacetyl chloride (2.2 mL, 0.02*M*), and triethylamine (2.3 mL, 0.02*M*), *N*-{4-[phenyldiazenyl]phenyl}-*N*-[phenylmethylene] amine (5.7g, 0.02*M*) (compound 2, stage IV_b) was added. After the completion of reaction (6 h), the reaction mixture was kept at room temperature for 30 min and then kept overnight in freezer. The precipitates so obtained were filtered, washed with water, and dried to obtain the crystals of 3-chloro-4-phenyl-1-{4-[phenyl diazenyl]phenyl}azetidin-2-one. Physical characteristics and structural assignments of all the synthesized compounds are exhibited in Table 1.

Stage D: Synthesis of 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one {4a–j}. 3-Chloro-4-phenyl-1-{4-[phenyldiazenyl]phenyl}azetidin-2-one **{3}** (1.97 g, 0.01*M*) in benzene (1000 mL) was irradiated in a Pyrex vessel with 350-nm UV light in a photochemical reactor for 8 h with magnetic stirring. Benzene was evaporated using a rotatory evaporator followed by the addition of acetone (30 mL) to dissolve unreacted compound. Yellow shiny crystals of 3-chloro-1-(4a,10b-diazaphenanthrene-2-yl)-4-phenyl azetidin-2-one **{4}** were obtained upon vacuum filtration. Overall illustration of procedure is depicted in Scheme 1. Physical characteristics and structural assignments of all the synthesized compounds are exhibited as follows:

3-Chloro-1-(4a,10b-diazaphenanthrenes)-4-phenylazetidin-2-ones{4a}. IR (υ, cm^1); 3365 (NH_{asy}), 3290 (NH_{sym}), 3080 (C—H, sp^2), 2010 (N═N), 1765 (C═O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 525 (C—Cl). ^{1}H NMR (δ, ppm): 6.1 (s, CH, four-membered ring), 7.1 (s, 10H, C_6H_5 × 2), 7.4–7.6 (d, 4H, Ar-H). Yield 82%, m. p. 126–27°C. Analytical data calculated for $C_{21}H_{16}N_3OCl$: % C: 69.99 (69.71), %H: 4.31 (4.46), %N: 11.55 (11.61).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(3′-chloro)-phenylazetidin-2-ones{4b}. IR (υ, cm^1); 3365 (NH_{asy}), 3290 (NH_{sym}), 3080 (C—H, sp^2), 2010 (N═N), 1765 (C═O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 525 (C—Cl). ^{1}H NMR (δ, ppm): 6.1 (s, CH, four-membered ring), 7.1 (s, 10H, C_6H_5 × 2), 7.4–7.6 (d, 4H, Ar-H). Yield 82%, m.p. 126–27°C. Analytical data calculated for $C_{21}H_{13}N_3OCl_2$: %C: 63.98 (64.01), % H: 3.32 (3.46), %N: 10.66 (10.76).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(4′-chloro)-phenylazetidin-2-ones{4c}. IR (υ, cm^1); 3371 (NH_{asy}), 3292 (NH_{sym}), 3080 (C—H, sp^2), 2010 (N═N), 1765 (C═O, four-membered), 1600, 1505, 1395 (C⋯⋯C, ring stretching), 810, 745 (subphenyl), 525 (C—Cl). ^{1}H NMR (δ, ppm): 6.16 (s, CH, four-membered ring), 7.23 (s, 10H, C_6H_5 × 2), 7.1–7.9 (d, 4H, Ar-H). Yield 78%, m.p. 129–130°C. Analytical data calculated for $C_{21}H_{13}N_3OCl_2$: %C: 63.98 (64.01), %H: 3.32 (3.46), %N: 10.66 (10.76).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(3′-hydroxy)-phenylazetidin-2-ones{4d}. IR (υ, cm^1); 3365 (NH_{asy}), 3290 (NH_{sym}), 3396 (bs, O—H), 3088 (C—H, sp^2), 2019 (N═N), 1761 (C═O, four-membered), 1603, 1567, 1390 (C⋯⋯C, ring stretching), 821, 757 (subphenyl), 609 (C—Cl). ^{1}H NMR (δ, ppm): 5.42 (s, CH, four-membered ring), 7.1 (s, 10H, C_6H_5 × 2), 7.3–7.9 (d, 4H, Ar-H). Yield 88%, m.p. 121–25°C. Analytical data calculated for $C_{21}H_{14}N_3O_2Cl$: %C: 67.12 (67.27), %H: 3.75 (3.86), %N: 11.18 (11.26).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(3′-ethyl)-phenylazetidin-2-ones{4e}. IR (υ, cm^1); 3364 (NH_{asy}), 3298 (NH_{sym}), 3083 (C—H, sp^2), 2011 (N═N), 1763 (C═O, four-membered), 1598, 1509, 1385 (C⋯⋯C, ring stretching), 818, 765 (subphenyl), 545 (C—Cl). ^{1}H NMR (δ, ppm): 5.2 (s, CH, four-membered ring), 7.23–8.12 (s, 10H, C_6H_5 × 2), 7.1–7.7 (d, 4H, Ar-H), 1.59 (q, 2H, CH_2), 1.26 (t, 3H, CH_3). Yield 87%, m.p. 122–25°C. Analytical data calculated for $C_{23}H_{18}N_3OCl$: %C: 71.22 (71.47), %H: 4.68 (4.76), %N: 10.83 (10.96).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(4′-ethyl)-phenylazetidin-2-ones{4f}. IR (υ, cm^1); 3360 (NH_{asy}), 3298 (NH_{sym}), 3083 (C—H, sp^2), 2011 (N═N), 1763 (C═O, four-membered), 1598, 1509, 1385 (C⋯⋯C, ring stretching), 818, 765 (subphenyl), 545 (C—Cl). ^{1}H NMR (δ, ppm): 5.2 (s, CH, four-membered ring), 7.21–8.12 (s, 10H, C_6H_5 × 2), 7.1–7.7 (d, 4H, Ar-H), 1.62q, 2H, CH_2), 1.24 (t, 3H, CH_3). Yield 81%, m.p. 122–25°C. Analytical data calculated for $C_{23}H_{18}N_3OCl$: %C: 71.22 (71.47), %H: 4.68 (4.76), %N: 10.83 (10.96).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(4′-nitro)-phenylazetidin-2-ones{4g}. IR (υ, cm^1); 3358 (NH_{asy}), 3289 (NH_{sym}), 3070 (C—H, sp^2), 2016 (N═N), 1775 (C═O, four-membered), 1608, 1505, 1385 (C⋯⋯C, ring stretching), 1336 (NO_2), 817, 765 (subphenyl), 545 (C—Cl). ^{1}H NMR (δ, ppm): 5.24 (s, CH, four-membered ring), 6.69–8.37 (s, 10H, C_6H_5 × 2), 7.08–7.21 (d, 4H, Ar-H). Yield 88%, m.p. 127–29°C. Analytical data calculated for $C_{21}H_{13}N_4O_3Cl$: %C: 62.31 (62.54), % H: 3.24 (3.45), % N:13.86 (13.94).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(3′-methyl)-phenylazetidin-2-ones{4h}. IR (υ, cm^1); 3369 (NH_{asy}), 3295 (NH_{sym}), 3084 (C—H, sp^2), 2012 (N═N), 1780 (C═O, four-membered), 1600, 1500, 1392 (C⋯⋯C, ring stretching), 811,

755 (subphenyl), 537 (C—Cl). ^{1}H NMR (δ, ppm): 5.18 (s, CH, four-membered ring), 7.1–8.14 (s, 10H, C_6H_5 × 2), 7.0–7.21 (d, 4H, Ar-H), 2.35 (s, 3H, CH_3). Yield 89%, m.p. 126–27° C. Analytical data calculated for $C_{22}H_{16}N_3OCl$: %C: 70.68 (70.71), %H: 4.31 (4.40), %N:11.24 (11.32).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(4′-methyl)-phenylazetidin-2-ones{4i}. IR (υ, cm^1); 3369 (NH_{asy}), 3295 (NH_{sym}), 3084 (C—H, sp^2), 2012 (N=N), 1780 (C=O, four-membered), 1600, 1500, 1392 (C⋯C, ring stretching), 811, 755 (subphenyl), 537 (C—Cl). ^{1}H NMR (δ, ppm): 5.18 (s, CH, four-membered ring), 6.91–8.17 (s, 10H, C_6H_5 × 2), 7.1–7.27 (d, 4H, Ar-H), 2.31 (s, 3H, CH_3). Yield: 91%, m.p. 27°C. Analytical data calculated for C_{22} $H_{16}N_3OCl$: %C: 70.68 (70.71), % H: 4.31 (4.40), %N: 11.24 (11.32).

3-Chloro-1-(4a,10b-diazaphenanthren-2-yl)-4-(3′-methoxy)-phenylazetidin-2-ones{4j}. IR (υ, cm^1); 3358 (NH_{asy}), 3294 (NH_{sym}), 3089 (C—H, sp^2), 2027 (N=N), 1760 (C=O, four-membered), 1600, 1500, 1391 (C⋯C, ring stretching), 1110 (C—O), 981, 785 (subphenyl), 615 (C—Cl). ^{1}H NMR (δ, ppm): 5.56 (s, CH, four-membered ring), 6.91–8.17 (s, 10H, C_6H_5 × 2), 7.4–7.8 (d, 4H, Ar-H), 3.73 (s, 3H, CH_3). Yield 88%, m.p. 132–35°C. Analytical data calculated for $C_{22}H_{16}N_3O_2Cl$: %C: 67.78 (67.86), %H: 4.14 (4.26), % N:10.78 (10.86).

Anti-inflammatory activity. ***Carrageenan-induced paw edema.*** Animals were housed in separate cages, six animals each, in temperature-controlled rooms at 25 °C. Animals were allowed for free access to food and water and were maintained at a 12-h light/dark cycle. Work was conducted in accordance with the internationally accepted principles for laboratory animals use of anti-inflammatory activities, all test compounds and reference drugs were suspended in 5% solution of gum acacia in normal saline. Suspensions of the test compounds, reference drugs, and 5% gum acacia-saline solution (negative control) were injected 1 mL each *i.p*. The anti-inflammatory activity of nine representatives of the synthesized compounds was evaluated according to the method described by Winter *et al*. [24], where a pedal inflammation in rat paws was induced by subplantar injection of 0.2-mL carrageenan (0.2%) suspension in gum acacia into the right hind of the rats.

Male adult albino rats (100–120 g) were divided into groups, 11 groups altogether, of five animals each. The rat paw thickness was measured with a vernier caliper (SMIEC, China) before and 1 h after the carrageenan injection to detect the carrageenan-induced inflammation. Each test compound at a dose of 10 mg kg^{-1} was injected *i.p*. to a separate group of rats 1 h after carrageenan injection. Control group received the vehicle (5% gum acacia), while the reference group received indomethacin, 10 mg kg^{-1}.

The difference between the thicknesses of the two paws was taken as a measure of edema. The measurement was carried out at 0, 1, 2, 3, and 5 h after injection of the test compounds, reference drug, and the vehicle. The results of anti-inflammatory activity of the test compounds and the reference drug are listed in Table 2.

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