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Synthesis and biological studies of carbonitrile derivatives from benzosuberones

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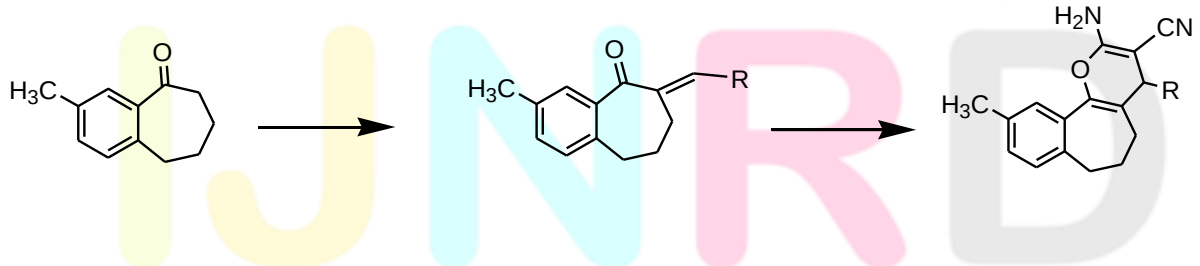
Abstract

2-Amino-4-(4-methoxy-phenyl)-10-methyl-4,5,6,7-tetrahydro-1-oxa-dibenzo[a,c]cycloheptene-3-carbonitrile derivatives (**3a-f**) obtained from 6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H* benzo[a]cyclohepten-5-ones (**2a-f**) with Cycloaddition of melanonitrile and aluminum oxide in DMF. **2a-f** were obtained by the condensation of 3,methyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones (**1**) with appropriate aromatic aldehydes.

Graphical Abstract



Key words
Benzosuberone, Amine, Carboniriles, Fungicides, Bactericide, Anti-cancer, Anti-diabetic.

Introduction

Structurally diverse nitrile-containing drugs are in use for a variety of medical treatments. The prevalence of nitrile-containing pharmaceuticals, and the continued stream of potential agents in the clinic, attests to the biocompatibility of nitrile functionality[1]. Vildagliptin drug have amino nitrile groups containing anti-diabetic activity[2]. Nitriles are unusual functionalities by virtue of the short, polarized triple bond[3]. The linear, rod-like geometry has a cylindrical diameter of 3.6 A for the pi system[4]. Resulting in a minuscule steric demand along the axis. For comparison, the CN unit is essentially eight times smaller than a methyl group[5]. Several crystal structures show the nittrile projecting into narrow clefts to

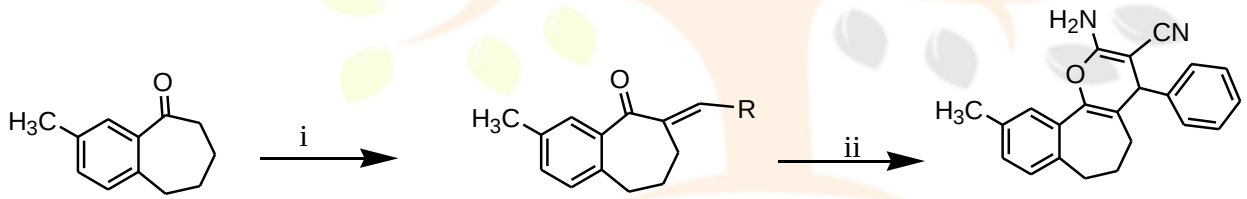
make polar interactions or hydrogen bonds in sterically congested environments[6]. Chalcones are potential biocides as some benzosuberone chalcones and their biological activity due to the α,β unsaturated carbonyl group. Chalcone are associated with wide range of biological activities[7]. Chalcone being a very good synthon, variety of novel heterocycles compounds can be designed with good pharmacological profile.

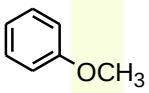
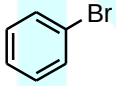
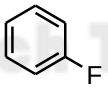
Prompted by these observations and in continuation of our work on the synthesis of biologically active nitrogen and sulfur containing heterocycles[8-12], we report in this paper the conversion of 6-arylidene-3-dimethyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones (**1a-g**) into derivatives of a new heterocyclic system containing amino-nitrile moiety and these compounds **2a-f** were prepared by adopting procedure reported [13&14]. The required starting compound 3,-methy-6,7,8,9-tetrahydrobenzo cyclohepten-5-one (**1**) was prepared starting from δ-(p-toloyl)valeric acid.

Results and Discussion

6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H* benzo[a]cyclohepten-5-ones (**2a-f**) were obtained by the condensation of 3-dimethyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones (**1**) with appropriate aromatic aldehydes. In the Amino Carbonitrile **3a-f**, the olefinic proton =CH-Ar appeared at δ 7.80 in their ^{1}H NMR spectra.

Cyclo addition of **2a-f** with melano nitrile in DMF yielded 2-Amino-4-(4-methoxy-phenyl)-10-meethyl-1-oxo-4,5,6,7-tetrahydro-1*H*-dienzo[a,c]cyclohepene-3-carbonitrile
derivatives **3a-f**. The IR spectra of **3a-f** exhibited a band due to 2190 (CN) cm^{-1}; 3280 cm^{-1} (NH_2) respectively, which indicates the presence of keto, amine and nitrile groups on the moity. Further, in their ^{1}H NMR spectrum, disappearance of the olefinic proton (=CH-Ar) at δ 7.80 and appearance of a single proton at δ 4.05 (1H, s, 4-H) and presence of amine at δ 4.5-4.95 (2H, bs) confirms the presence of flavonoid ring contains amine and nitrile groups. The proton signals of methyl group and aliphatic protons appeared at expected region.



R = 1)  2) 3) 4) 5)  6) 

i) = alcoholic KOH and apropriate aldehyde
ii) = melanonitrile, DMF and Al_2O_3

Experimental

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer; 1H NMR in CDCl3 on a Varian FT-80A spectrometer with TMS as an internal standard; and mass spectra on a VG-micro mass 7070H mass spectrometer. TLC was run on Silica gel G coated plates and iodine vapor as visualizing agent.

Compound 3a-f General procedure

A mixture of 6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[a] cyclohepten-5-ones **2a** (0.0007 mole), melanonitrile (0.0007 mole) and aluminum oxide-potassium fluoride (5 gr) in DMF solution (10 mL) was heated under reflux for 4 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue was added to ice water (15 mL). The resulting solution was extracted with chloroform (20 mL). Upon evaporations, the organic layer gave the crude product, which was purified by preparative TLC using 10% ethyl acetate-petroleum ether afforded products

Compound 3a (2-Amino-4-(4-methoxy-phenyl)-10-methyl-4,5,6,7-

tetrahydro-1-oxa-dibenzo[a,c]cycloheptene-3-carbonitrile) : Yield: 75%; m.p. 68-69^{0}C; IR (KBr): 2190 (CN) cm^{-1}; 3280 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.65-1.68 (2H, m, 6-CH_2), 1.95-1.99 (2H, m, 5-CH_2), 2.35 (3H, s, 10-CH_3), 2.55-2.78 (2H, m, 7-CH_2), 3.93 (3H, s, -OCH_3), 4.05 (1H, s, 4-H), 4.5-4.95 (2H, bs, -NH_2), and 6.65-7.05 (7H, m, Ar- CH); MS: m/z 357 ($M^{+\cdot}$); Anal. Found: C, 77.29; H, 5.85; N, 7.81; O,8.94. $C_{23}H_{21}O_2N_2$ requires C, 77.31; H, 5.88; N, 7.84; O,8.96.%.

Compound 3b (2-Amino-10-methyl-4-phenyl-4,5,6,7-

tetrahydro-1-oxa-dibenzo[a,c]cycloheptene-3-carbonitrile): Yield: 67%; m.p. 85-87^{0}C; IR (KBr): 2210 (CN) cm^{-1}; 3490 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.65-1.68 (2H, m, 6-CH_2), 1.94-1.96 (2H, m, 5-CH_2), 2.34 (3H, s, 10-CH_3), 2.60-2.78 (2H, m, 7-CH_2), 4.14 (1H, s, 4-H), 4.5-4.95 (2H, bs, -NH_2), and 6.89-7.07 (7H, m, Ar-CH); MS: m/z 327 ($M^{+\cdot}$); Anal. Found: C, 80.70; H, 5.78; N, 8.53, O, 4.85. $C_{22}H_{19}N_2O$ requires C, 80.73; H, 5.81; N, 8.56, O, 4.89%.

Compound 3c (2-Amino-10-methyl-4-thiophen-2-yl-4,5,6,7-

tetrahydro-1-oxa-dibezo[a,cycloheptene-3-carbonitrile): Yield: 75%; m.p. 80-85^{0}C; IR (KBr): 2200 (CN) cm^{-1}; 3380 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.63-1.65 (2H, m, 6-CH_2), 1.95-1.99 (2H, m, 5-CH_2), 2.33 (3H, s, 10-CH_3), 2.55-2.78 (2H, m, 7-CH_2), 4.03 (3H, s, -OCH_3), 4.10 (1H, s, 4-H), 4.6-4.97 (2H, bs, -NH_2), and 6.65-7.05 (6H, m, Ar-CH); MS: m/z 334($M^{+\cdot}$); Anal. Found: C, 71.83; H, 5.35; N, 8.35; S, 9.56; O,4.62. $C_{20}H_{18}ON_2S$ requires C, 71.85; H, 5.38; N, 8.38; S, 9.58; O,4.79.%.

Compound 3d (2-Amino-10-methyl-4-pyridin-4-yl-4-5,6,7-

tetrahydro-1oxa-dibezo[*a,c*]cycloheptene-3-carbonitrile): Yield: 62%; m.p. 78-80^{0}C; IR (KBr): 2280 (CN) cm^{-1}; 3680 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.64-1.68 (2H, m, 6-CH_2), 1.94-1.96 (2H, m, 5-CH_2), 2.34 (3H, s, 10-CH_3), 2.55-2.58 (2H, m, 7-CH_2), 4.14 (1H, s, 4-H), 4.65-4.85 (2H, bs, -NH_2), and 6.89-8.60 (7H, m, Ar-CH); MS: m/z 329 ($M^{+\cdot}$); Anal. Found: C, 77.56; H, 5.74; N, 12.68; O,4.83. $C_{21}H_{19}N_3O$ requires C, 76.59; H, 5.77; N, 12.70; O,4.86.%.

Compound 3e (2-Amino-4-(4-bromo-phenyl)-10-methyl-4,5,6,7-

tetrahydro-1-oxa-dibenzo[*a,c,*]cycloheptene-3-carbonitrile): Yield: 63%; m.p. 67-69^{0}C; IR (KBr): 2170 (CN) cm^{-1}; 3390 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.66-1.68 (2H, m, 6-CH_2), 1.95-1.96 (2H, m, 5-CH_2), 2.35 (3H, s, 10-CH_3), 2.65-2.78 (2H, m, 7-CH_2), 4.10 (1H, s, 4-H), 4.5-4.95 (2H, bs, -NH_2), and 6.89-7.31 (7H, m, Ar-CH); MS: m/z 407 ($M^{+\cdot}$); Anal. Found: C, 64.83; H, 4.63; N, 6.84; O, 3.90; Br,19.62. $C_{22}H_{19}N_2OBr$
Requires C, 64.86; H, 4.66; N, 6.87; O, 3.93; Br,19.65.%.

Compound 3f (2-amino-4-(4-fluoro-phenyl)-10-methyl-4,5,6,7-

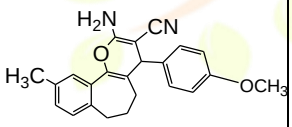
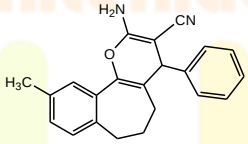
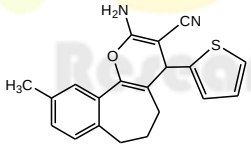
tetrahydro-1oxa-dibezo[*a,c*]cycloheptene-3-carbonitrile): Yield: 60%; m.p. 94-96^{0}C; IR (KBr): 2180 (CN) cm^{-1}; 3380 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.66-1.68 (2H, m, 6-CH_2), 1.95-1.96 (2H, m, 5-CH_2), 2.35 (3H, s, 10-CH_3), 2.65-2.78 (2H, m, 7-CH_2), 4.10 (1H, s, 4-

H), 4.5-4.95 (2H, bs, -NH_2), and 6.65-7.05 (7H, m, Ar-CH); MS: m/z 358 ($M^{+\cdot}$); Anal. Found: C, 76.30; H, 5.47; N, 8.06; O,4.59; F,5.45. $C_{22}H_{19}N_2OF$ requires C, 76.30; H, 5.49; N, 8.09; O,4.62, F,5.49.%.

Compound 3g (2-Amino-10-methyl-4-p-tolyl-4,5,6,7-

tetrahydro-1oxa-dibenzo[a,c]cycloheptene-3-carbonitrile) Yield: 62%; m.p. 70-72^{0}C; IR (KBr): 2170 (CN) cm^{-1}; 3390 cm^{-1} (NH_2) ^{1}H NMR ($CDCl_3$): δ 1.66-1.68 (2H, m, 6-CH_2), 1.95-1.96 (2H, m, 5-CH_2), 2.35 (6H, s, Ar-CH_3 & 10-CH_3), 2.65-2.78 (2H, m, 7-CH_2), 4.13 (1H, s, 4-H), 4.5-4.95 (2H, bs, -NH_2), and 6.89-7.05 (7H, m, Ar-CH); MS: m/z 354 ($M^{+\cdot}$); Anal. Found: C, 80.68; H,5.34; N, 8.15,O,4.64 $C_{23}H_{22}N_2O$ requires C, 80.70; H, 52.38; N, 8.18, O, 4.67 %.

Pharmacological results

S.NO.	STRUCTURE	ANALGESIC ACTION (% PROTECTION)		ANTIINFLMMATORY ACTIVITY (% INHIBITION OF EDEMA)	ANTIBACTERIAL ACTIVITY	
		TAIL CLIP	WRITHING		STAPHYLOCOCCUS	E.COLI/KLEBSIELLA
3a		110	20	40	4	8
3b		13	12	26	2	3.5
3c		117	13	45	6	10

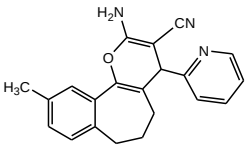
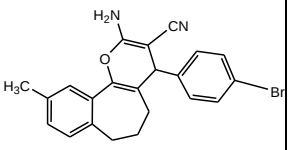
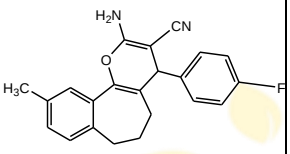
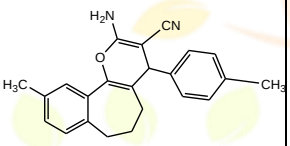
3d		113	15	38	5	8
3e		13	14	36	5	7
3f		90	15	45	8	12
3g		15	16	3	2	4
	Aspirin	555	46	17		
	Phenylbutazone	30	20	39		
	Rifampicin				8	13

Table-I

Conclusion

Based on the wide range of various biological activities of benzosuberone derivatives and emergence of multidrug resistance of the continued use of antibacterial and antifungal of different microorganisms, we synthesized herein a new serious of benzosuberone derivatives and we thought these molecules will give better results. Most of our molecules have been observed the high rate of anti-inflammatory activity than anti-bacterial activity (Table-I).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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