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Synthesis, Characterization and Anticonvulsant Activity of Novel Benzyl-6-Chloro Indole Carboxylate Derivatives

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Abstract: Indole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. In the present study some novel indole carboxylate derivatives were synthesized under green synthesis by microwave irradiation method according to the scheme. Methyl 6-chloro-1Hindole-5-carboxylate was treated with benzyl chloride in presence of CS_2CO_3 in dry DMF. Then methyl 1-benzyl-6-chloro-1H-indole-5-carboxylate was treated with oxalyl chloride in dry DCM and different secondary amines to get methyl 1-benzyl-6-chloro-3-[(N,N-dialkylamino)(oxo)acetyl]-1H-indole-5-carboxylates derivatives (IND-1 to IND-10). The synthesized newer indole carboxylate derivatives have been characterized by using elemental analysis, FT-IR, ^{1}HNMR, ^{13}C NMR spectroscopy and further supported by Mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique. All the synthesized compounds were evaluated for anticonvulsant activity by maximal electroshock method (MES) by using phenytoin as standard at a concentration of 30 mg/kg. The anticonvulsant effect of the newly synthesized compounds was assessed by absence or reduction of hind limb tonic extensor phase. Among the synthesized derivatives compounds IND-5 and IND-10 were found to be the most potent compounds in the series.

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INTRODUCTION

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole alkaloids have been proved to be medicinally important natural compounds. Indole compounds include the plant hormone Auxin, the anti-inflammatory drug indomethacin, the β-blocker pindolol, and the naturally occurring hallucinogen dimethyltryptamine. The indole skeleton is one of the most attractive frameworks with a wide range of biological and pharmacological activities. This physiologically important nucleus is abundantly found in therapeutic agents as well as in natural products. Many researchers have described synthesis of indole and its derivatives along with its applications in literature. A large number of heterocyclic compounds containing the indole ring are associated with diverse pharmacological properties such as analgesic (Rajashree S Chavan*et al*, 2011), antiallergic (Mahadevan*et al*, 2013), antibacterial (Olga N. Burchak*et al*, 2011), anticonvulsant (Priya Ahuja and Nadeem Siddiqui, 2014 & Anil Kumar *et al*, 2011), antifungal (Mhaske*et al*, 2014), antihistaminic (M. Sarangapani*et al*, 2010), anti-inflammatory (Ashok Kumar *et al*, 2010 & R.S. Chavan*et al.*, 2010), anticancer (Hardik M. Patel *et al*, 2012 &SaundaneAnandRaghunath, *et al* 2014), antiviral (Adel A.-H. Abdel-Rahman et al, 2012), anthelminthic (K. S. Nataraj*et al*, 2010), antihypertensive (Monge Vega *et al*, 2006), and antioxidant (Hamid Khaledi*et al*, 2011) activities. Thus the efficient synthesis of novel substituted indole carboxylate derivatives still represent highly pursued target.

EXPERIMENTAL:

Material and Methods:

All the chemicals used were of laboratory grade and procured from E. Merck, Germany; Qualigens, Mumbai; Sigma Aldrich, USA and S.D. Fine Chemicals, Mumbai. Melting points were determined in digital melting point apparatus and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV

light. All compounds were purified by recrystallization with suitable organic solvents. All the microwave experiments were performed using RAGA's microwave synthesizer. IR spectra were recorded on BROOKER-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in $CDCl_3$ solution on a BRUKER Ac 400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Purity of the synthesized compounds was checked by HPLC AGILENT. The results are in agreements with the structures assigned. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use. All the synthesized compounds are evaluated for anticonvulsant activity by using maximal electroshock method (MES). The seizures were induced by SECOR INDIA electro convulsiometer.

Preparation of Methyl 1-benzyl-6-chloro-1*H*-indole-5-carboxylate: To a stirred suspension of CS_2CO_3 (2.72 g, 0.02 mol) and methyl 6-chloro-1*H*indole-5-carboxylate (2.09 gm, 0.01 mol) in dry DMF (10 ml), after 5.0 minute benzylchloride (1.14 ml, 0.01 mol) was added drop wise. The resultant solution was stirred for 5hour at room temperature, and poured onto crushed ice, the product was isolated andwashed with water and hexane to give pure product. Yield: 94 %, M.P 70-72 ^{0}C.

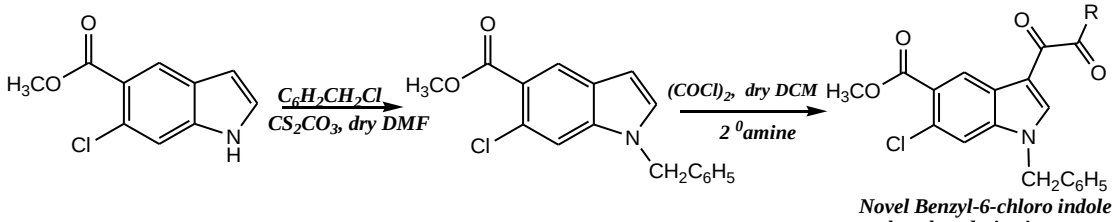
General procedure for the preparation of Methyl 1-benzyl-6-chloro-3-[(*N*,*N*-dialkylamino) (oxo)acetyl]-1*H*-indole-5-carboxylates: To a stirred cooled (ice bath) solution of methyl 1-benzyl-6-chloro-1*H*-indole-5-carboxylate (0.5 gm, 1.67 mmol) in dry DCM (12 ml), oxalyl chloride (0.71 ml, 8.35 mmol)was added dropwise in solution. The obtained solution was stirred at 0 ^{0}C for 30.0 minuteand then at 25-30 ^{0}C for 1 hour. Dark yellow colored was formed. The solvent was removed *in vacuo*, the residue was dissolved in dry DCM (12 ml) then add different secondary amine (5.01 mmol) was added drop wise. The reaction mixture was stirred at 0^{0}C for 30.0 minute and then 25-30 ^{0}C for another 30.0 minutes (monitored by TLC). Thesolvent was removed *in vacuo*. The product was dissolved in water and extracted with ethylacetate (25 ml × 3). The combined organic layers were washed with water followedby brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the solid was triturated with hexane and resulting precipitate was filtered, washed withhexane and dried to give analytical pure product. The physical constants of the productare recorder in Table-1**.**

Methyl 1-benzyl-6-chloro-3-[(diethylamino)(oxo)acetyl]-1H-indole-5-carboxylate(IND-1):M.P 78-80 ^{0}C; Purity by HPLC: 96 %; IR (KBr): 3038 (Ar, C-H str), 2983 (C-H str), 1725 (ketone, C=O str), 1629 (amide, C=O str), 1519 (Ar, C=C str), 1447 (Ar, C=C str), 1256(C-H ban), 1165 (C-N str), 780 (C-Clstr) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.18-1.31 (m, 6H, $2CH_3$), 3.33-3.40 (q, *J*=6.96 Hz, 2H, CH_2), 3.48-3.55 (q, *J*=7.08 Hz, 2H,CH_2), 3.95 (s, 3H, OCH_3), 5.36 (s, 2H, CH_2), 7.13-7.16 (m, 2H, ArH), 7.34-7.38 (m, 4H,ArH), 7.95 (s, 1H, ArH), 8.85 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 12.77,14.41, 39.38, 42.46, 51.26, 52.40, 112.79, 114.42, 124.56, 125.09, 125.96, 126.95,128.68, 129.26, 134.37, 138.63, 139.92, 163.26, 166.49, 185.31; MS: *m/z* = 426 $[M]^+$;Anal. Calcd for $C_{23}H_{23}ClN_2O_4$: C, 64.71; H, 5.43; N, 6.56. Found: C, 64.44; H, 5.29; N,6.41%.

Table 1: Physical constants of novel benzyl-6-chloro indole carboxylate derivatives

Compd	R	M.F	M.W	Yield (%)	M.P (^{0}C)	R_f
IND-1	Diethylamino	$C_{23}H_{23}ClN_2O_4$	426.89	83	102-104	0.51
IND-2	Morpholin-4-yl	$C_{23}H_{21}ClN_2O_5$	440.87	79	110-112	0.42
IND-3	Piperidin-1-yl	$C_{24}H_{23}ClN_2O_4$	438.90	85	140-141	0.35
IND-4	4-Methylpiperazin-1-yl	$C_{24}H_{24}ClN_3O_4$	453.91	84	107-109	0.44
IND-5	4-Ethylpiperazin-1-yl	$C_{25}H_{26}ClN_3O_4$	467.94	86	190-191	0.46
IND-6	4-Phenylpiperazin-1-yl	$C_{29}H_{26}ClN_3O_4$	515.99	78	160-161	0.32
IND-7	Dipropan-2-ylamino	$C_{25}H_{27}ClN_2O_4$	454.94	82	120-122	0.40
IND-8	Pyrrolidin-1-yl	$C_{23}H_{21}ClN_2O_4$	424.87	84	165-167	0.43
IND-9	2-Methylpiperidin-1-yl	$C_{25}H_{25}ClN_2O_4$	452.93	81	170-171	0.37
IND-10	4-Methylpiperidin-1-yl	$C_{25}H_{25}ClN_2O_4$	452.93	82	173-175	0.36

Scheme 1: Synthesis of novel benzyl-6-chloro indole carboxylate derivatives



Novel Benzyl-6-chloro indole carboxylate derivatives (IND-1 to IND-10)

Methyl 1-benzyl-6-chloro-3-[morpholin-4-yl(oxo)acetyl]-1H-indole-5-carboxylate (IND-2): M.P 98-99 ^{0}C; IR (KBr): 3072, 2975, 2926, 1708, 1632, 1547, 1460, 1262, 788 cm^{-1}; MS:*m/z* = 440 $[M]^+$; Anal. Calcd for $C_{23}H_{21}ClN_2O_5$: C, 62.66; H, 4.80; N, 6.35. Found: C,62.20; H, 4.70; N, 6.22%.

Methyl 1-benzyl-6-chloro-3-[oxo(piperidin-1-yl)acetyl]-1H-indole-5-carboxylate (IND-3). M.P 135-137 ^{0}C; IR (KBr): 3048, 2968, 2937, 1715, 1645, 1536, 1450, 1278, 756 cm^{-1};MS: *m/z* = 438 $[M]^+$; Anal. Calcd for $C_{24}H_{23}ClN_2O_4$: C, 65.68; H, 5.28; N, 6.38. Found:C, 65.26; H, 5.20; N, 6.23%.

Methyl1-benzyl-6-chloro-3-[(4-methylpiperazin-1-yl)(oxo) acetyl]-1H-indole-5-carboxylate (IND-4).M.P 103-105 ^{0}C; IR (KBr): 3065, 2945, 2891, 1720, 1635, 1555, 1468, 1246,760 cm-1; MS: *m/z* = 454 $[M+1]^+$; Anal. Calcd for $C_{24}H_{24}ClN_3O_4$: C, 63.50; H, 5.33; N,9.26. Found: C, 63.05; H, 5.20; N, 9.07%.

Methyl 1-benzyl-6-chloro-3-[(4-ethylpiperazin-1-yl)(oxo)acetyl]-1H-indole-5-carboxylate (IND-5*).* M.P 170-171 ^{0}C; IR (KBr): 2996, 2975, 2944, 1727, 1635, 1529, 1464, 1240, 771cm^{-1}; MS: *m/z* = 468 $[M+1]^+$; Anal. Calcd for $C_{25}H_{26}ClN_3O_4$: C, 64.17; H, 5.60; N, 8.98.Found: C, 63.83; H, 5.58; N, 8.79%.

Methyl1-benzyl-6-chloro-3-[oxo(4-phenyl piperazin-1-yl)acetyl]-1H-indole-5-carboxylate (IND-6).M.P 113-115 ^{0}C; IR (KBr): 3031, 2947, 2905, 1726, 1642, 1525, 1499, 1239, 759 cm^{-1}; MS: *m/z* = 467 $[M]^+$; Anal. Calcd for $C_{29}H_{26}ClN_3O_4$: C, 67.50; H, 5.08; N, 8.14.Found: C, 67.19; H, 4.95; N, 7.94%.

Methyl1-benzyl-6-chloro-3-[(dipropan-2-ylamino)(oxo)acetyl]-1H-indole-5-carboxylate (IND-7).M.P 104-106 ^{0}C; IR (KBr): 3038, 2979, 2948, 1728, 1638, 1525, 1447, 1253, 778cm^{-1}; MS: *m/z* = 454 $[M]^+$; Anal. Calcd for $C_{25}H_{27}ClN_2O_4$: C, 66.00; H, 5.98; N, 6.16.Found: C, 65.56; H, 5.87; N, 6.01%.

Methyl 1-benzyl-6-chloro-3-[oxo(pyrrolidin-1-yl)acetyl]-1H-indole-5-carboxylate (IND-8). M.P 142-144 ^{0}C; Purity by HPLC: 93 %; IR (KBr): 3109, 2981, 2959, 1723, 1618, 1524,1448, 1254, 781 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.91-2.02 (m, 4H, 2CH2),3.58-3.63 (t, *J*=6.60 Hz, 2H, CH_2), 3.68-3.73 (t, *J*=6.40 Hz, 2H, CH_2), 3.95 (s, 3H,OCH_3), 5.32 (s, 2H, CH_2), 7.15-7.17 (m, 2H, ArH), 7.33-7.38 (m, 4H, ArH), 8.34 (s, 1H,ArH), 8.90 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 19.57, 20.51, 46.19, 47.55,51.27, 52.39, 112.75, 114.26, 124.18, 125.06, 126.08, 126.95, 128.30, 129.24, 134.59,138.47, 141.16, 163.73, 166.50, 184.43; MS: *m/z* = 424 $[M]^+$; Anal. Calcd for$C_{23}H_{21}ClN_2O_4$: C, 65.02; H, 4.98; N, 6.59. Found: C, 64.70; H, 4.83; N, 6.44%.

Methyl 1-benzyl-6-chloro-3-[(2-methylpiperidin-1-yl)(oxo)acetyl]-1H-indole-5-carboxylate (IND-9).M.P 90-92 ^{0}C; IR (KBr): 3040, 2950, 2918, 1719, 1633, 1521, 1458, 1260, 768cm^{-1}; MS: *m/z* = 452 $[M]^+$; Anal. Calcd for $C_{25}H_{25}ClN_2O_4$: C, 66.29; H, 5.56; N, 6.18.Found: C, 65.96; H, 5.46; N, 6.02%.

Methyl 1-benzyl-6-chloro-3-[(4-methylpiperidin-1-yl)(oxo)acetyl]-1H-indole-5-carboxylate (IND-10).M.P 181-183 ^{0}C; IR (KBr): 3016, 2976, 2922, 1710, 1632, 1510, 1444, 1240, 765cm^{-1}; MS: *m/z* = 452 $[M]^+$; Anal. Calcd for $C_{25}H_{25}ClN_2O_4$: C, 66.29; H, 5.56; N, 6.18.Found: C, 65.93; H, 5.42; N, 6.03%.

BIOLOGICAL EVALUATION:

ANTICONVULSANT ACTIVITY:

Anticonvulsant activity was performed by MES (maximal electroshock method). This method has been approved by the Institutional Animal Ethical Committee at Chalapathi Institute of Pharmaceutical Aciences, Guntur (Ref. No. IAEC/CIPS/08/2015-16). In the MES method, adult male and female Albino rats (Wistar strain) weighing 100-200 gm were used. The animals were divided into three groups (control, standard and test) and each group comprising of three rats. The test compounds were suspended in 1% aqueous CMC suspension and were injected i.p. in doses ranging from 15, 30 and 60 mg/kg body weight. Phenytoin sodium was used as a standard drug which was given in the dose of 30 mg/kg by i.p. which was observed to protect 100% against the induced convulsions. The control group received only 1% aqueous CMC suspension. The seizures were induced by electro convulsiometer (SECOR INDIA, Scientific Engg. Corp; New Delhi). The animals were subjected to electroshock by delivering the current of 150 mA through the corneal electrodes for a period of 0.2 seconds. The animals were observed for 30 min convulsive responses. Different stages of convulsions i.e. the tonic flexion (towards the upper extremities), tonic extensor phase (extension of the lower extremities), clonic convulsions (intermediate jerking of limbs), stupor (unconsciousness) and recovery or death were observed for each animal (data as shown in Table 2). The anticonvulsant effect of newly synthesized compounds was assessed by absence or reduction of hind limb tonic extensor phase. Each value represents the mean SEM (standard error mean) of three rats significantly different from standard drug phenytoin (ttab < tcal, P < 0.05) (student's t-test).

Table 2: Anticonvulsant activity of novel benzyl-6-chloro indole carboxylate derivatives

Compd	30 mg/kg (Dose)				
	Flexion (mean±SEM)	**Extensor (mean±SEM)**	**Clonus (mean±SEM)**	**Stupor (mean±SEM)**	**Recovery / Death**
IND-1	4.6±0.5	11.6±0.5	13.3±0.4	112.1±0.4	R
IND-2	5.1±0.4	7.2±0.2	11.8±0.6	110.7±0.4	R
IND-3	4.1±0.4	7.4±0.9	10.1±0.7	110.4±0.4	R
IND-4	4.9±0.2	8.4±0.6	12.3±0.9	114.1±0.6	R
IND-5	4.2±0.7	6.5±0.5	7.6±0.1	108.3±0.7	R
IND-6	5.1±0.9	8.8±0.4	12.8±0.4	112.5±0.2	R
IND-7	3.7±0.5	8.4±0.2	11.2±0.9	110.6±0.1	R
IND-8	5.3±0.5	9.1±0.3	10.8±0.4	118.6±0.7	R
IND-9	5.8±0.4	6.8±0.5	13.3±0.4	118.2±0.8	R
IND-10	3.6±0.4	6.2±0.9	7.2±0.4	106.1±0.9	R
Control	4.2±0.9	9.6±0.4	11.8±0.2	114.1±0.4	R
Phenytoin sodium	Absent	5.6±0.2	2.4±0.1	104.2±0.2	R

Phenytoin sodium (30 mg/kg i.p.)

RESULTS AND DISCUSSION:

In the present research work Methyl 6-chloro-1Hindole-5-carboxylate was treated with benzyl chloride in presence of CS_2CO_3 in dry DMF. Then methyl 1-benzyl-6-chloro-1H-indole-5-carboxylate was treated with oxalyl chloride in dry DCM and different secondary amines to get the methyl 1-benzyl-6-chloro-3-[(N,N-dialkylamino)(oxo)acetyl]-1H-indole-5-carboxylates derivatives (IND-1 to IND-10). All newly synthesized compounds were characterized on the basis of their M.P, R_f value (data are shown in Table-1), FTIR, ^{1}H NMR, ^{13}C NMR, MASS spectra and elemental analysis. Anticonvulsant activity of the compounds was performed using the maximal electroshock-induced seizure (MES) method in albino rats (Wistar strain) of either sex. This method claimed to detect compounds possessing activity against generalized tonic clonic (grandmal) seizures. The MES test is a measure of an anticonvulsant drug to abolish or reduce the time of the tonic extensor component of the hind limb in the maximal seizure pattern induced by 150 mA of current delivered for 0.2 seconds. In the primary MES screening compound IND-3, IND-5, IND-7 and IND-10 afforded protection against seizures confirming their potential utility as prototypic molecules. The anticonvulsant activity data revealed that all the compounds showed remarkable reduction of hind limb tonic extensor phase when given in the dose of 30 mg/kg i.p. and compounds IND-3 and IND-10 were found to be the most potent compounds in the series. Moreover, anticonvulsant activity of the other tested compounds was found to be much less effective than phenytoin used as standard anticonvulsant drug.

CONCLUSION:

Result of present study demonstrate that, a new class of some novel indole carboxylate derivatives were synthesized and evaluated as anticonvulsant agents. The newly synthesized heterocyclics exhibited promising anticonvulsant activity using MES method. The anticonvulsant studies showed significant activity compared to standard. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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