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SYNTHESIS, CHARACTERIZATION AND COMPARATIVE SCREENING OF SOME NEWER 2-PHENYL INDOLE AND 5-CHLORO-2-PHENYL INDOLE DERIVATIVES

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ABSTRACT
Biologically active phenyl indole and chloro phenyl indole derivatives were efficiently synthesized. The reaction of 2-phenyl-1H-indole **A** and 5-chloro-2-phenyl-1H-indole **B**, with chloroacetylchloride yielded 2-chloro-1-(2-phenyl-1H-indol-1yl)ethanone **1** and 2-chloro-1-(5-chloro-2-phenyl-1H-indol-1-yl)ethanone **4** respectively. Compound **1** and **4** on Friedal Crafts cyclization in presence of aluminium chloride and nitrobenzene yielded indolo[2,1-α]isoquinolin-6(5H)-one **2** and 10-chloroindolo [2,1-α]isoquinolin-6(5H)-one **5** respectively, which upon hydrolysis afforded 2-(2-(1H-indol-2-yl)phenyl)acetic acid **3** and 2-(2-(5-chloro-1H-indol-2-yl) phenyl) acetic acid **6** respectively. The newly designed compounds were characterized on the basis of spectral studies and screened for anti-inflammatory and anti-microbial activities.
KEYWORDS: 2-phenyl-indole, 5-chloro-2-phenyl-indole, Friedal Crafts cyclization.

RESUMO
Derivados de fenil indol e clorofenil indol, biologicamente ativos, foram sintetizados de maneira eficiente. A reação de 2-fenil- 1H-indol e 5-cloro-2-fenil-1H-indole com cloreto de cloroacetila seguida por ciclização Friedel Crafts levou aos compostos **2** e **5**, respectivamnete, os quais depois de hidrólise formaram 2-(2-(1H-indol-2-il)ácido fenilacético,3, e 2-(2-(5-cloro-1H-indol-2-il) ácido fenilacético, **6**. Os compostos foram caracterizados e a atividade antiinflamatória e antimicrobial foram avaliadas.
PALAVRAS CHAVE: 2-Fenil indol, 5-Cloro-2-fenil indol, Ciclização Friedel Crafts

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INTRODUCTION

The statistical data provided that the global pharmaceutical market *grew to 712 billion* US dollars *in 2007* at a rate of *10.7% and is* expected to grow to 929 billion US dollars by 2012, which consists of 25.5 billion dollars of NSAIDS market. The global anti-infective market is currently valued at 66.5 *billion* US dollars with antibacterial agents accounting for over 50% of sales. Indole and phenyl acetic acid derivatives are known to have potent anti –inflammatory (1), anti-microbial (2) and analgesic (3) activities. As per prospects of NSAIDS in global pharmaceutical market and literary evidences for activities associated with indoles, an attempt was made to generate novel potent anti-inflammatory and anti-microbial drugs by converting a 2-phenyl indole moiety **A** and 5-chloro-2- phenyl indole moiety **B** into some novel 2-(2-(1H-indol-2-yl)phenyl)acetic acid **3** and 2-(2-(5-chloro-1H-indol-2-yl) phenyl) acetic acid **6.** During this pathway of synthesis of 2-chloro-1-(2-phenyl-1H-indol-1yl)ethanone **1**, indolo[2,1-α]isoquinolin-6(5H)-one **2**, 2-chloro-1-(5-chloro-2-phenyl-1H-indol-1yl)ethanone **4** and10-chloroindolo [2,1-α]isoquinolin-6(5H)-one **5** were obtained as key intermediates. All the newly designed compounds were further characterized and evaluated for anti-inflammatory and anti-microbial activities.

EXPERIMENTAL

Melting points of newly designed compounds were determined in open capillary tubes. IR spectra were recorded (in KBr) on Perkin Elmer and 1HNMR spectra on Bruker, SF 300 instruments. Purity of designed compounds was checked by TLC on aluminium sheets with silica gel 60 F254 (0.2 mm).

2-chloro-1-(2-phenyl-1H-indol-1yl)ethanone (1)
To a solution of 2-phenyl-1H-indole **A** (0.01 mol) in methyl ethyl ketone, a solution of chloro acetyl chloride (in methyl ethyl ketone) was added dropwise on a magnetic stirrer. During the reaction to maintain the pH 8-9 a solution of sodium carbonate (in distilled water) was also added dropwise. The stirring was continued for further 75 min. From the resultant mixture the organic layer was separated and subjected for distillation under reduced pressure. The obtained crude product was recrystallized from methanol to yield compound **1**.
IR (KBr, cm^{-1}): 2916 (C-H of CH_2), 3020 (C-H of aromatic ring), 1662 (C=O of amide)
^{1}HNMR (CDCl3, ppm): 4.88 (2H; s; CH_2), 6.53 (1H; s; H_3), 7.05-7.29 (3H; m; H_5, H_6 & H_4'), 7.31-7.46 (5H; m; H_7, H_2', H_3', H_5', H_6'), 7.6 (1H; m; H_4)
MS (m/z): 269 (M^+), 233, 76, 51

indolo[2,1-α]isoquinolin-6(5H)-one (2)
To a solution of 2-chloro-1-(2-phenyl-1H-indol-1yl)ethanone **1** in nitrobenzene, 1g of powdered aluminium chloride was added in small portions with simultaneous stirring for 15 min. The reaction mixture was further stirred continuously for 1 hr. The resultant mixture was transferred onto crushed ice to form a semisolid mass, which was subjected to distillation to remove nitrobenzene to get a solid product. The obtained crude product was recrystallized from methanol to yield compound **2**

IR (KBr, cm-1): 2922 (C-H of CH_2), 3045 (C-H of aromatic ring), 1668 (C=O of amide)
^{1}HNMR (CDCl3, ppm): 3.66 (2H, s, CH_2), 6.61 (1H; s; H_3), 6.8-7.24 (5H; m; H_5, H_6 H_3', H_4', & H_5'), 7.29-7.67 (3H; m; H_4, H_5, H_2')
MS (m/z): 233 (M^+), 76, 51

2-(2-(1H-indol-2-yl)phenyl)acetic acid (3)
A mixture of indolo[2,1-α]isoquinolin-6(5H)-one **2** in ethanol and sodium hydroxide solution was refluxed for 6 hrs. The resultant reaction mixture was filtered and to the filtrate HCl was added drop wise to yield a solid mass. The crude product so obtained was filtered and recrystallized from methanol to yield 2-(2-(1H-indol-2-yl)phenyl)acetic acid **3**.
IR (KBr, cm-1): 3447 (O-H of COOH), 3021 (C-H of aromatic ring), 2930 (C-H of methylene), 1721 (C=O of COOH),
^{1}HNMR (CDCl3, ppm): 8.52 (1H, s, N-H), 3.42 (2H, s, CH_2), 6.51 (1H, s, H_3), 6.82-7.19 (5H; m; H_5, H_6, H_3', H_4', H_5'), 7.29-7.64 (3H, m; H_2', H_7, H_4), 11.2 (1H, s, O-H)
MS (m/z): 251 (M^+), 234, 233, 224, 206, 91, 76, 51, 45

2-chloro-1-(5-chloro-2-phenyl-1H-indol-1yl)ethanone (4)
To a solution of 5-chloro-2-phenyl-1H-indole A (0.01 mol) in methyl ethyl ketone, a solution of chloro acetyl chloride (in methyl ethyl ketone) was added dropwise on a magnetic stirrer. During the reaction to maintain the pH 8-9 a solution of sodium carbonate (in distilled water) was also added drop wise. The stirring was continued for further 75 min. From the resultant mixture the organic layer was separated and subjected for distillation under reduced pressure. The obtained crude product was recrystallized from methanol to yield compound **4**.
IR (KBr, cm-1): 2919 (C-H of CH_2), 3028 (C-H of aromatic ring), 1664 (C=O of amide)
^{1}HNMR (CDCl3, ppm): 4.92 (2H; s; CH_2), 6.59 (1H; s; H_3), 7.14-7.34 (3H; m; H_5, H_6 & H_4'), 7.39-7.49 (5H; m; H_7, H_2', H_3', H_5', H_6'), 7.54 (1H; d; j=2.7, H_4)
MS (m/z): 303 (M^+), 267, 76, 51

10-chloroindolo [2,1-α]isoquinolin-6(5H)-one (5)
To a solution of 2-chloro-1-(5-chloro-2-phenyl-1H-indol-1yl)ethanone **4** in nitrobenzene, 1g of powdered aluminium chloride was added in small portions with simultaneous stirring for 15 min. The reaction mixture was further stirred continuously for 1 hr. The resultant mixture was transferred onto crushed ice to form a semisolid mass, which was subjected to distillation to remove nitrobenzene to get a solid product. The obtained crude product was recrystallized from methanol to yield compound **5**.
IR (KBr, cm-1): 2930 (C-H of CH_2), 3049 (C-H of aromatic ring), 1674 (C=O of amide)
^{1}HNMR (CDCl3, ppm): 3.72 (2H, s, CH_2), 6.68 (1H; s; H_3), 6.94-7.28 (5H; m; H_5, H_6 H_3', H_4', & H_5'), 7.36-7.48 (2H; m; H_5, H_2'), 7.56 (1H; d; j=2.6, H_4)
MS (m/z): 267 (M^+), 231, 91, 76, 51

2-(2-(5-chloro-1H-indol-2-yl) phenyl) acetic acid (6)
A mixture of 10-chloroindolo [2,1-α]isoquinolin-6(5H)-one **5** in ethanol and sodium hydroxide solution was refluxed for 6 hrs. The resultant reaction mixture was filtered

and to the filtrate HCl was added drop wise to yield a solid mass. The crude product so obtained was filtered and recrystallized from methanol to yield 2-(2-(5-chloro-1H-indol-2-yl) phenyl) acetic acid **6**.

IR (KBr, cm-1): 3458 (O-H of COOH), 3028 (C-H of aromatic ring), 2942 (C-H of methylene), 1716 (C=O of COOH)

^{1}HNMR (CDCl3, ppm): 8.65 (1H, s, N-H), 3.52 (2H, s, CH_2), 6.47 (1H, s, H_3), 6.93-7.14 (4H; m; H_6, H_3', H_4', H_5') 7.32-7.38 (2H; m; H_7, H_2') 7.62 (1H; d; J = 2.8, H_4), 11.35 (1H; s, O-H)

MS (m/z): 285 (M^+), 268, 267, 258, 249, 240, 91, 76, 51, 45

Biological activity

The designed compounds **1, 2, 3, 4, 5, 6** were screened for anti-inflammatory activity by carageenan induced paw oedema method using distilled water as solvent. The results were recorded using indomethacin as standard drug and are given in table-II. The designed compounds **1-6** were also were screened for antibacterial and antifungal activity using disk diffusion method. The results were recorded using amoxicillin and egriseofulvin as standard drugs respectively and are given in Table-III and Table-IV.

RESULTS AND DISCUSSION

2-chloro-1-(2-phenyl-1H-indol-1yl)ethanone **1** and 2-chloro-1-(5-chloro-2-phenyl-1H-indol-1-yl)ethanone **4**, prepared from 2-phenyl-1H-indole **A** and 5-chloro-2-phenyl-1H-indole **B** respectively. The obtained compounds **1** and **4** when cyclized with aluminium chloride yielded indolo[2,1-α]isoquinolin-6(5H)-one **2** and 10-chloroindolo [2,1-α]isoquinolin-6(5H)-one **5** respectively, which on hydrolysis lead to potent anti-inflammatory 2-(2-(1H-indol-2-yl)phenyl)acetic acid **3** and 2-(2-(1H-indol-2-yl)phenyl)acetic acid **6** respectively. The synthetic procedure for conversion of compound **A to 3** and **B to 6** is suggested in Scheme 1 and 2. Physical data of **1-6** are given in Table I. The assigned structure, molecular formulae and the anomeric configuration of the newly designed compounds **1-3** and **4- 6** were further confirmed and supported by mass, 1H-NMR and IR spectral data, based on occurrence of molecular ion peak of the assigned structures, downfield shifting of protons and different stretching bands of the compounds. The resultant compounds 1, 2, 3, 4, 5 and 6 after characterizations were further screened for anti-inflammatory and anti-microbial activity (data given in Table-II, III and IV).

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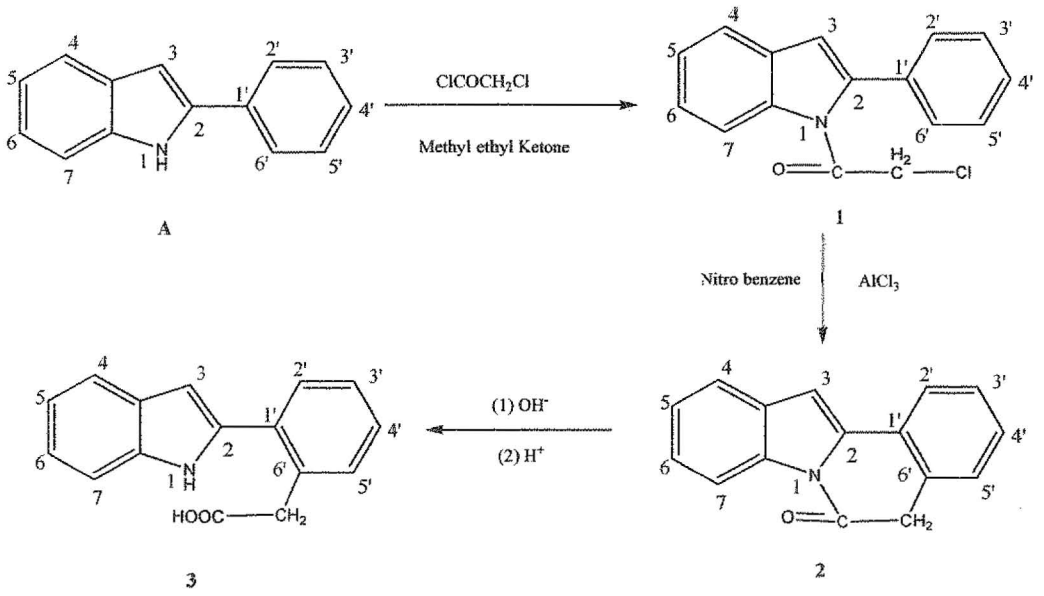
Scheme1



Scheme 2

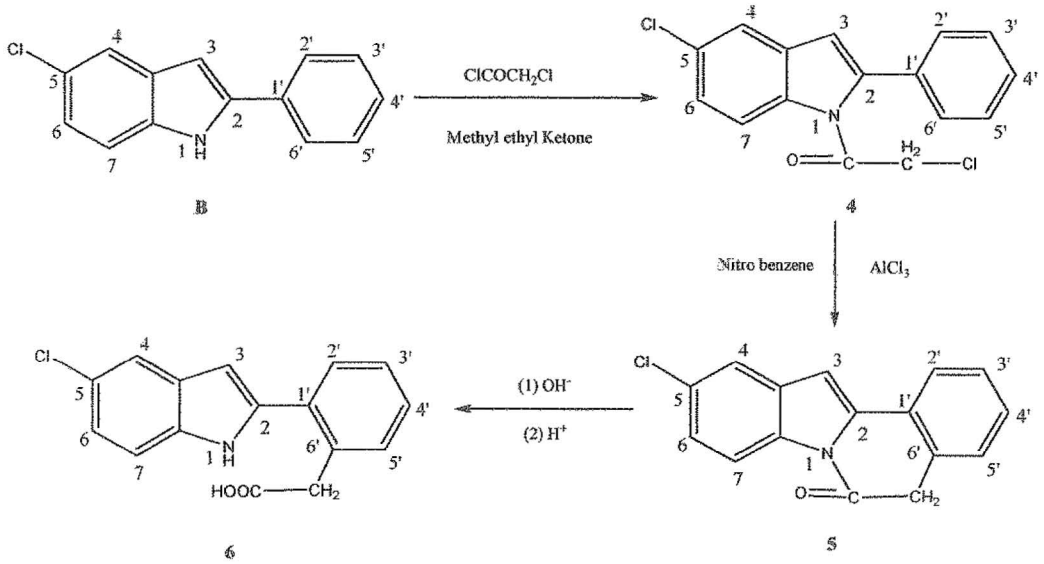


Table I. Physical data of compounds

Compound No.	Physical characteristics	Yield (%)	Molecular formula	Mol. Wt.	M.P. (°C)	R_f Value
1	White crystals	82	$C_{16}H_{12}ClNO$	269.73	205-206	0.56
2	White crystals	76	$C_{16}H_{11}NO$	233.26	212-213	0.42
3	White crystals	73	$C_{16}H_{13}NO_2$	251.28	228-229	0.38
4	White crystals	74	$C_{16}H_{11}Cl_2NO$	304.17	217-218	0.52
5	White crystals	68	$C_{16}H_{10}ClNO$	267.71	223-224	0.46
6	White crystals	64	$C_{16}H_{12}ClNO_2$	285.72	231-232	0.34

TABLE II- Anti-inflammatory activity of 2-phenyl indole and 5-chloro-2-phenyl indole derivatives on carrageenan-induced paw oedema in rats.

Compd 20mg/po	Paw volume in ml, mean ±SD(% inhibition of paw edema)			
	After 1hr	After 2hr	After 3hr	After 4hr
Control	0.880±0.0179	0.886±0.0163	0.897±0.0151	0.885±0.0242
Indomethacin	0.368±0.0197 (58.18%)*	0.326±0.0163 (63.2%)*	0.290±0.0219 (67.67)*	0.265±0.0350 (70.05%)*
1	0.847±0.0242 (3.75%)	0.833±0.0273 (5.98%)	0.803±0.029 (10.47%)	0.790±0.0452 (10.73%)
2	0.840±0.0219 (4.45%)	0.817±0.0151 (7.78%)	0.787±0.0350 (12.26%)	0.757±0.0234 (14.46%)
3	0.583±0.0408 (33.75%)*	0.557±0.0197 (37.13%)*	0.527±0.0350 (41.24%)*	0.503±0.067 (43.16%)*
4	0.817±0.0388 (7.15%)	0.793±0.0273 (10.4%)	0.773±0.0350 (13.8%)	0.737±0.0151 (16.7%)
5	0.663±0.0344 (25.79%)*	0.647±0.0266 (27.2%)*	0.615±0.0253 (31.43%)*	0.595±0.0179 (32.95%)*
6	0.540±0.057** (38.63%)	0.515±0.0210** (41.8%)	0.395±0.0283** (55.96%)	0.325±0.0266** (63.27%)

*p<0.05 vs control, **p<0.01 vs control (n=6)

Table: III – Antibacterial-sensitivity testing of 1-6.

Compd. No.	Antibacterial Activity		
	Zone of Inhibition (mm)		
	S. aureus	***E. coli***	***P. aeruginosa***
1	14.3 ± 0.33	18.3 ± 0.33	14.3 ± 0.33
2	20.7 ± 0.67	12 ± 0.00	16.7 ± 0.33
3	21.7 ± 0.67	16 ± 0.00	17.7 ± 0.33
4	16.7 ± 0.67	18 ± 0.00	14.7 ± 0.67
5	22.3 ± 0.67	17.7 ± 0.33	12 ± 0.00
6	23 ± 0.00	18.3 ± 0.33	20.7 ± 0.33
Amoxicillin	26 ± 0.54	25 ± 0.68	26 ± 2.4
DMF	-	-	-

- All the values are expressed as mean ± SEM of triplicates

Table: IV– Antifungal-sensitivity testing of 1-6.

Compd. No.	Antifungal Activity		
	Zone of Inhibition (mm)		
	C. albicans	***A. flavus***	***A. fumigates***
1	10.3 ± 0.33	8 ± 0.00	9 ± 0.00
2	9 ± 0.00	11 ± 0.00	10 ± 0.00
3	10 ± 0.00	11 ± 0.00	8 ± 0.00
4	8 ± 0.00	11.7 ± 0.67	9 ± 0.00
5	10.3 ± 0.33	12 ± 0.00	9.3 ± 0.33
6	14 ± 0.00	13 ± 0.00	9 ± 0.00
Griseofulvin	24± 0.00	25 ± 0.00	23 ± 0.00
DMF	-	-	-

- All the values are expressed as mean ± SEM of triplicates

CONCLUSIONS

After screening the designed compounds for anti-inflammatory and anti-microbial (anti-bacterial and anti-fungal) studies it was found that each compound **1-3** and **4-6** possesses anti-inflammatory activity and anti-microbial activity to certain extent. Among the newly synthesized derivatives, compound **6** have shown significant ($p<0.01$) anti-inflammatory activity and was found to be almost equipotent to indomethacin when tested on rats. The compounds **3** and **5** have also shown significant ($p<0.05$) results. The other tested compounds **1, 2 and 4** have also shown anti-inflammatory activity to certain extent. Anti-microbial (anti-bacterial and anti-fungal) screening revealed that among the newly synthesized derivatives, compound **6** have shown the most significant anti-microbial activity when compared to standard drugs. Compound **5, 3 and 2** were found to have moderate activity while compound **1** and **4** were found to have mild activity among the tested compounds. After comparing the anti-inflammatory activity, anti-microbial activity and structural configuration of compounds **1-3** and **4-6**, it was concluded that the incorporation of chlorine in derived compounds enhances their activity.

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