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Anti-inflammatory, analgesic, anticonvulsant and antimicrobial activities of some newly synthesized N-alkyl-3- indolyl pyrimidines and benzimidazolo(1,2-a) pyrimidines

A series of new N-alkyl-3-indolyl pyrimidines 2a-h, thiopyrimidines 3a-h and benzimidazolo(1,2-a)pyrimidines 5a-h were prepared and evaluated for their anti-inflammatory, analgesic, anticonvulsant and antimicrobial activities. The most potent anti-inflammatory active compound of these series is 3f which showed inhibition of oedema 84 % compared with reference drugs flufenamic acid and indomethacin which showed inhibition of 53 and 51%, respectively. Compounds 2f, 3e and 3f showed analgesic protection of 100 % compared with reference drug flufenamic acid which showed protection of 83 %, also, exhibited higher anticonvulsant activity, that is, 66, 83 and 83 % than the reference drug diazepam which showed protection of 50 %. Moreover, the new compounds showed remarkable antibacterial activity against Gram-negative bacteria E. coli and P. aeruginosa at 100 µg/disk.

Keywords:indole, pyrimidine, anti-inflammatory, analgesic, anticonvulsant, antimicrobial.

INTRODUCTION

Indomethacin is non-steroidal anti-inflammatory drug (NSAIDs) and has been shown to exert anti-inflammatory effect {1}. Indole, the potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties as, anti-inflammatory {2-4}, analgesic {5}, anticonvulsant {6, 7} antibacterial and antifungal activities {8, 9}. Besides these, pyrimidine derivatives comprise a diverse and interesting group of drugs {10, 11}, some are antiviral agents {12}, the others are selective cholecystokinin subtype 1 (CCK1) receptor antagonists {13}, antimicrobial agents {14} and a few are antiinflammatory {15, 16}. In the light of these interesting biological activities, the goal of this work is the synthesis of some new pyrimidine, and benzimidazolo(1,2-a) pyrimidines incorporated to the N-alkyl indole for evaluating their anti-inflammatory, analgesic, anticonvulsant and antimicrobial activities hoping to obtain new compounds in high activity.

MATERIAL AND METHODS

Melting points were determined in open capillary tubes on Electrothermal 9100 digital melting point apparatus (Buchi) and are uncorrected. Microanalytical data were found within ± 0.4% of the theoretical values. IR spectra (KBr discs) were recorded on a Bruker Vector 22 infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured with Jeol 270 MHz (JEOL, Tokyo, Japan) spectrometer and NMR-drx500\u The ^{1}H NMR in DMSO-d_6 and chemical shift was recorded in δ ppm relative to TMS. Mass spectra (EI) were run at 70 eV with JEOL-JMS-AX500 and GCMS-QP1000Ex Schimadzu mass spectrometer (Japan).Indole-3-carboxaldehyde **1a** and N-alkyl indole-3-carboxaldehydes **1b-h** were prepared as in literature {17, 18}. N-alkyl-3-indolylidene malononitriles **4a, 4c** and **4d** were prepared according to previously reported procedures {19, 20}.

Chemistry

N-alkyl -3-[5-carbonitrile-2, 4-dioxo (2a-h) and 4-oxo-2-thioxo (3a-h) -pyrimidin-6-yl] indoles General Procedure- A mixture of aldehydes **1a-h** (0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol), urea and/or thiourea (0.01 mol) in absolute ethanol (20 mL) containing potassium carbonate (1.38 g, 0.01 mol) was refluxed for 4-5 h. After cooling, the reaction mixture was neutralized with dilute hydrochloric acid (1:1) and the formed solid was filtered off, washed with water, air dried and recrystallized from ethanol afforded **2a-h** and **3a-h**, respectively, (Scheme).

N-alkyl-3-indolylidene malononitriles(4a-h)

General procedure- To a solution of compounds **1a-h** (0.01 mol) in absolute ethanol (20 mL) malononitrile (0.66 g, 0.01 mol) and triethyl amine (0.5 mL) was added. The reaction mixture was stirred vigorously for 1-3 h. and then left overnight at room temperature. The solid that formed was filtered off, washed with water, air dried and recrystallized from ethanol to give **4a-h**.

N-Alkyl-3-[3-amino-4-carbonitrile benzimidazolo(1, 2-a)pyrimidin-5-yl] indoles (5a-h).

General procedure- To a solution of 2-aminobenzimidazole (1.33 g, 0.01 mol) in absolute ethanol (20 mL) and triethylamine (0.5 mL), was added indolylidene malononitriles **4a-h** (0.01 mol) and the reaction mixture was refluxed for 2-3 h. After cooling, the solid which formed filtered off, air dried and recrystallized from ethanol to give **5a-h**.

Biological assay

Animals

Animals were obtained from the animal house colony of the National Research Centre, Cairo, Egypt. All animals were allowed free access to water and were kept on a constant standard diet. All procedures involving animals were carried out in accordance with the guide for the care and use of laboratory animals (National Academy of Science of Egypt) and were approved by the Animals Studies Committee at Washington University. Adult male albino rats, weighing 150–180 g, were fasted for 12 hours and used for determining the anti-inflammatory activity. Adult Swiss Webster mice of both sexes, weighing 20–25 g, were fasted

for 12–24 hours and used for determining the analgesic and anticonvulsant activities.

Evaluation of anti-inflammatory activity – The inhibitory activity of the studied compounds on carrageenean-induced rat's paw oedema was determined according to the method of Obkowicz et al. {21}. Groups of adult male albino rats (150–180 g), 8 animals each, were orally dosed with tested compounds at a dose of 20 and 5 mg kg^{-1} one hour before carrageenean challenge. Foot paw oedema was induced by subplantar injection of 0.05 mL of 1% suspension of carrageenean in saline into the plantar tissue of one hind paw. An equal volume of saline was injected into the other hind paw and served as control. Four hours after drug administration the animals were decapitated, blood was collected and the paws were rapidly excised. The average weight of edema was estimated for the treated as well as for the control group and the percentage inhibition of oedema was evaluated {22}. Flufenamic acid and indomethacin (20 and 5 mg kg^{-1}) were used as standard reference against the test compounds.

Statistical analysis: Data are expressed as means ± SE. In anti-inflammatory study data are expressed as means ± SE. The results of carrageenean-induced paw edema are expressed as percentage of change to the control (pre-drug) values. Differences between vehicle control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by the Duncan's multiple range tests. A probability value < 0.05 was considered statistically significant.

Evaluation of analgesic activity: The method of Okun et al. {23} was used to induce writhing in this study. A sensitivity test was carried out one day before drug administration where the animals were infected (i. p.) with with 0.2 - 0.25 mL of 0.02 % freshly prepared solution of p-benzoquinone in distilled water. Animals showing writhing to p-benzoquinone within 30 minutes were chosen for studying the analgesic activity. On the next day, mice were divided into 13 groups each of 6 animals, and the drugs were administered according to the following protocol, one group received 2% Tween 80 (control), second group received flufenamic acid received 20 mg/kg (reference), and the third group received indomethacine 5 mg/kg (reference), while the other groups received two doses of the tested compounds, 50 and 25 mg kg^{-1}. One hour later, 0.02% solution of p-benzoquinone was administrated (i. p.). The animals were observed for 30 minutes after injection of the irritant during which the animals showing writhing were counted (writhing is defined as stretch, torsion to one side, drawing up of hind leg, retraction of the abdomen, so that the belly of mouse touches the floor). Any writhing is considered as a positive response. The analgesic activity was expressed as the protection (%).

Evaluation of anticonvulsant activity: Mice of both sexes weighing 20-25g were used and injected intrapertoneally with 2% Tween 80 (control) and 5 mg kg^{-1} diazepam (reference drug), and the other groups were received two doses 25 and 12.5 mg kg^{-1}. One hour after the drug administration, animals were stimulated through ear electrode of 50 mA as a signal stimulator for 0.2 s. {24}. The characteristic of electric shock seizure are a tonic limb flexion of 1 to 2 sec., followed by a tonic limb extension of roughly 10 to 12 s., and finally generalized clonic movement for 12 sec. Only abolishing of the hind limb tonic extensor spasm is recorded as the measure of anticonvulsant potency. The tonic component is considered abolished if the hind leg extension does not exceed a 900 with the plane of the body. Animals in each group, showing protection against convulsion were counted. The anticonvulsant activity was expressed as the protection (%).

Evaluation of antimicrobial activity: The antimicrobial activity of the synthesized compounds was determined in vitro by using the disc diffusion method {25, 26} against a variety of pathogenic microorganism Escherichia coli, Pseudomonas aeruginosa (Gram-negative bacteria) Staphylococcus aureus, Bacillus cereus (Gram-positive bacteria) and one strain of fungi (Candida albicans). They were isolated from clinical samples and identified to the species level according to different API systems (bioMerieux). The antimicrobial activity screening was performed using 25, 50 and 100 µg/disc in the Nutrient and MacConky agar media for bacteria and on Sabouraud Dextrose agar (Oxoid) for fungus. Dimethylformamide (DMF) was used as solvent which showed no inhibition zones. The inhibition zones of the tested compounds were measured in (mm). Cefotaxime and Piperacillin were used as reference drugs for bacteria. Nystatin [(30 unit) manufactured by Bristol-Myers Squibb, Giza, Egypt, [European unit = 0.04 µg] for fungus used as reference drugs.

RESULTS AND DISCUSSION

On continuation of our work to synthesized a novel pyrimidine derivatives {27} here in the starting compounds N-alkylindole-3-carboxaldehydes **1a-h** were condensed with ethyl cyanoacetate and urea in the presence of potassium carbonate to give N-alkyl-3-(5-carbonitrile-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-yl) indoles **2a-h** (Scheme). Whereas, compounds **1a-h** on refluxing with ethyl cyanoacetate and thiourea in the presence of potassium carbonate yielded N-alkyl-3-(5-carbonitrile-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-6-yl) indoles **3a-h** (Scheme). Compounds **2a** and **3a** are previously reported {17}. The structures of compounds **(2b-h)** and **(3b-h)** were confirmed by their correct elemental analyses **Table (I)** and spectral data (IR, NMR and mass) **Table (II)**. The IR (KBr) of compounds **(2b-h)** showed absorption bands in ranging 1665–1742 cm^{-1} characteristic for (C=O) groups, while compounds **(3b-h)** showed an additional absorption bands in ranging 1254–1275 cm^{-1} characteristic for (C=S) groups.

On the other hand, base catalyzed reactions of N-alkylindole-3-carboxaldehydes **1a-h** with malononitrile gave the corresponding N-alkyl-3-indolylidene malononitriles **4a-h**. The reaction of the latter compounds with 2-aminobenzimidazole in refluxing ethanol and in the presence of base according to El-Gazzar {28} led to the formation of N-alkyl-3-[3-amino-4-carbonitrile-benzimidazolo(1,2-a)pyrimidin-5-yl] indoles **5a-h** in good yields 71 to 85% (Scheme). The structures of compounds **5a-h** were confirmed by their correct elemental analyses **Table (I)** and spectral data (IR, NMR and mass) **Table (II)**.

Anti-inflammatory-activity

All the newly synthesized compounds **2, 3** and **5a-h** were evaluated for their anti-inflammatory activity against carrageenean induced rat's paw oedema at 20 and 5 mg kg^{-1} (p. o.) using flufenamic acid and indomethacin as reference drugs 20 and 5 mg kg^{-1}, respectively. From the data

obtained **Table III**, compounds **2e, 2f, 2h, 3a, 3e, 3f, 3h, 5e** and **5f** exhibited anti-inflammatory activity ranging from 57 to 84 % in a dose of 20 mg kg^{-1} than the reference drug flufenamic acid in a dose of 20 mg kg^{-1}. Compounds **2f, 3f,** and **5f** with p-chloro substituent showed higher anti-inflammatory activity 69, 84 and 62 % than that the o-chloro substituent which showed 62, 62 and 57 % at a dose 20 mg kg^{-1}. The compounds with bromine atom at p-position **2h, 3h** and **5h** showed inhibition 69, 65 & 24 %, respectively at a dose 20 mg kg^{-1}; these activities are more or less than that the activities of compounds which have ortho or para chlorosubstituents. On the other hand, comparing the activity of the tested compounds with the reference drug indomethacin (5 mg kg^{-1}), compounds **2a, 3a, 5a, 2e, 2f, 5e** and **5h** showed lower activity and compounds **2h, 2e, 3f, 3h** and **5f** showed higher anti-inflammatory activity of 65, 57, 54, 57 and 54 %, respectively. The most potent anti-inflammatory active compound is **3f** in a dose 20mg kg^{-1} which showed inhibition of 84 % compared with reference drugs flufenamic acid and indomethacin in adose 20 and 5mg kg-1 which showed inhibition of 53 and 51% respectively.

Analgesic activity

The chosen compounds in a dose of 50 mg kg^{-1} showed remarkable analgesic activity **Table IV**. From the data obtained, compounds **2f, 3e** and **3f** showed higher activity with protection 100 % at a dose 50 mg kg^{-1} than the reference drug flufenamic acid 83 % at a dose of 20 mg kg^{-1}. Compounds with chloro atom **2e, 2f, 3f, 5e** and **5f** were found to have high analgesic activity of 66, 100, 100, 100, 83 and 83 % in a dose of 50 mg kg^{-1} and at a dose of 25 mg kg^{-1} they showed analgesic activity of 33, 50, 33, 50, 66 and 50 %, respectively. Compounds **5e** and **5f** which contain the benzimidazole ring showed protection 83 % in a dose 50 mg kg^{-1} but at a dose of 25 mg kg^{-1} they showed protection 66 and 50 %. The presence of benzimidazole moiety in these compounds did not increase the protection (%).

Anticonvulsant activity

From the data illustrated in **Table V**, it is found that, compounds **2f, 3e** and **3f** showed higher anticonvulsant activity 66, 83 and 83 %, respectively, at a dose of 25 mg kg^{-1} than the reference drug diazepam which showed 50 % at a dose 5 mg kg^{-1}. While, compounds **2e, 5e** and **5f** at a dose of 25 mg kg^{-1} showed equipotent anticonvulsant activity 50 % as the reference drug diazepam in a dose 5 mg kg^{-1}. On the other hand, only compound **3f** showed higher anticonvulsant activity 66 % at a dose 12.5 mg kg^{-1} than the reference drug diazepam 50 % in a dose 5 mg kg^{-1}.

Antimicrobial activity

The newly synthesized compounds were evaluated for their antimicrobial activity against two strains of Gram-negative and two strains of Gram-positive bacteria and one strain of fungi using the disk diffusion method at 100, 50 & 25 µg /disk, respectively. The results showed that, the tested compounds revealed remarkable antimicrobial activity reflected by their ability to inhibit Gram-negative bacteria E. coli and P. aeruginosa at 100 µg/disk, and showed moderate to slight activity towards Gram-positive bacteria S. aureus and B. cereus at 100 µg/disk. On the other hand, all the compounds under test showed slight to non sensitive towards the fungus C. albicans. The data obtained are given in **Table (VI)**.

CONCLUSIONS

The newly synthesized compounds revealed remarkable anti-inflammatory, analgesic, anticonvulsant and antimicrobial activities. The most potent anti-inflammatory active compound of these series is **3f** which showed inhibition of oedema 84 % compared with reference drugs flufenamic acid and indomethacin which showed inhibition of 53 and 51%, respectively. Compounds **2f, 3e** and **3f** showed analgesic protection of 100 % compared with reference drug flufenamic acid which showed protection of 83 % also, exhibited higher anticonvulsant activity, that is, 66, 83 and 83 % than the reference drug diazepam which showed protection of 50 %. Moreover, the compounds showed remarkable antibacterial activity against Gram-negative bacteria E. coli and P. aeruginosa at 100 µg/disk.

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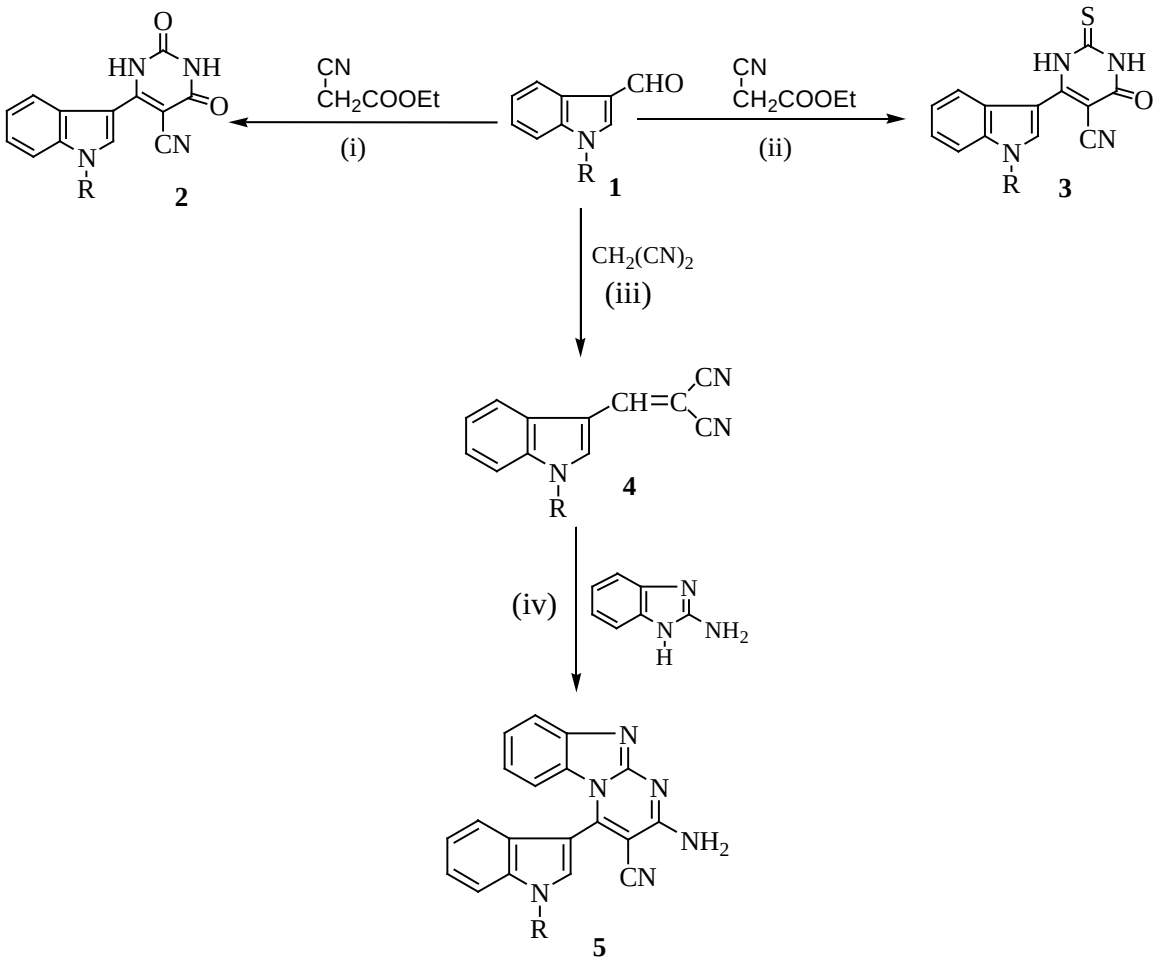

1-5	R
a	H
b	CH_2CH_3
c	$CH_2C_6H_5$
d	COC_6H_5
e	$COC_6H_4Cl_{(O)}$
f	$COC_6H_4Cl_{(p)}$
g	$SO_2C_6H_5$
h	$SO_2C_6H_4Br_{(p)}$

Scheme
Reagents and conditions: **(i)** urea, K_2CO_3, reflux, EtOH, **(ii)** thiourea, K_2CO_3, reflux, EtOH, **(iii)** Et_3N, reflux **(iv)** Et_3N, reflux.

Table I: physical and analytical data of the prepared compounds

Compd. No.	Molecular formula (M. Wt.)	M.P. (^oC)	Yield (%)	Analysis (%) (calculated / found)		
				C	H	N
2b	$C_{15}H_{12}N_4O_2$ (280)	170-72	82	64.28/64.11	4.28/4.00	20.00/20.22
2c	$C_{20}H_{14}N_4O_2$ (342)	198-200	85	70.17/70.00	4.09/3.99	16.37/16.11
2d	$C_{20}H_{12}N_4O_3$ (356)	210-12	80	67.41/67.21	3.37/3.21	15.73/15.66
2e	$C_{20}H_{11}CLN_4O_3$ (390.50)	218-20	75	61.45/61.22	2.81/2.66	14.34/14.21
2f	$C_{20}H_{11}CLN_4O_3$ (390.50)	138- 40	81	61.45/61.32	2.81/2.70	14.34/14.12
2g	$C_{19}H_{12}N_4O_4S$ (392)	227-29	80	58.16/58.00	3.06/3.12	14.28/14.11
2h	$C_{19}H_{11}BrN_4O_4S$ (471)	95-97	92	48.40/48.20	2.33/2.11	11.88/11.91
3b	$C_{15}H_{12}N_4OS$ (296)	97-99	70	60.81/60.70	4.05/3.99	18.91/18.79
3c	$C_{20}H_{14}N_4OS$ (358)	110-12	82	67.03/67.00	3.91/4.00	15.64/15.54
3d	$C_{20}H_{12}N_4O_2S$ (372)	137-39	75	64.51/64.33	3.22/3.44	15.05/15.21
3e	$C_{20}H_{11}ClN_4O_2S$ (406.5)	172-74	71	59.04/59.22	2.70/2.55	13.77/13.61
3f	$C_{20}H_{11}ClN_4O_2S$ (406.5)	140-42	70	59.04/59.21	2.70/2.81	13.77/13.95
3g	$C_{19}H_{12}N_4O_3S_2$ (408)	105-07	76	55.88/60.00	2.94/3.01	13.72/13.65
3h	$C_{19}H_{11}BrN_4O_3S_2$ (487)	90-92	79	46.81/45.66	2.25/2.41	11.49/11.51
4b	$C_{14}H_{11}N_3$ (221)	140-42	78	76.01/76.23	4.97/5.00	19.00/18.99
4e	$C_{19}H_{10}ClN_3O$ (331.5)	195-97	80	68.77/68.84	3.01/3.22	12.66/12.82
4f	$C_{19}H_{10}ClN_3O$ (331.5)	218-20	82	68.77/6854	3.01/2.98	12.66/12.44
4g	$C_{18}H_{11}N_3O_2S$ (333)	219-21	72	64.86/64.76	3.30/3.50	12.61/12.84
4h	$C_{18}H_{10}BrN_3O_2S$ (412)	224-26	70	52.42/52.61	2.42/2.54	10.19/10.41
5a	$C_{19}H_{12}N_6$ (324)	207-09	80	70.37/70.50	3.70/3.84	25.92/25.77
5b	$C_{21}H_{16}N_6$ (352)	153-55	78	71.59/71.66	4.54/4.66	23.86/23.68
5c	$C_{26}H_{18}N_6$ (414)	187-89	85	75.36/75.55	4.34/4.51	20.28/20.11
5d	$C_{26}H_{16}N_6O$ (428)	208- 10	72	72.89/72.90	3.73/3.80	19.62/19.55
5e	$C_{26}H_{15}ClN_6O$ (462.5)	193- 95	77	67.45/67.55	3.24/3.45	18.16/18.22
5f	$C_{26}H_{15}ClN_6O$ (462.5)	211-213	79	67.45/67.50	3.24/3.11	18.16/18.32
5g	$C_{25}H_{16}N_6O_2S$ (464)	143-145	71	64.65/64.80	3.44/3.62	18.10/18.22
5h	$C_{25}H_{15}BrN_6O_2S$ (543)	150- 52	74	55.24/55.44	2.76/2.81	15.46/15.32

Table II: Spectral characterization of the prepared compounds

Compd No.	IR (ν_{max} cm^{-1})	NMR (δ, ppm)		MS (*m/z*, %)
		^{1}H	^{13}C	
2b	3319 & 3140 (NH), 2213 (CN), 1698 (C=O), 1568 (C=C).	9.90 & 8.50 (2H, 2s, 2NH), 8.61 (1H, s, H-2 indole), 7.27-8.57 (4H, m, Ar-H), 4.33 (2H, q, CH_2), 1.41 (3H, t, CH_3).		-
2c	3402 & 3100 (NH), 2220 (CN), 1678 &1665 (C=O), 1570 (C=C).	13.3 & 9.94 (2H, 2s, 2NH), 8.69 (1H, s, H-2 indole), 7.63-8.52 (4H, m, Ar-H of indole), 7.31 (5H, s, Ar-H of phenyl), 5.67 (2H, s, CH_2-N).	49.86(CH_2-N), 111.37-137.43 (Ar-C), 166.58 & 185.57 (2C=O).	342 (M^+, 20), 91 (100)
2d	3314 & 3282 (NH), 2213 (CN), 1695 (C=O), 1566 (C=C).	13.1 & 9.9 (2H, 2s, 2NH), 8.7 (1H, s, H-2 indole), 7.1-8.2 (9H, m, Ar-H).	114 (CN), 112, 118-166 (Ar-C), 180 & 185 (2C=O).	356 (M^+, 20), 193 (100)
2e	3271 (NH), 2220 (CN), 1682 (C=O), 1563 (C=C), 718 (Cl).	12.0 & 10.3 (2H, 2s, 2NH), 7.0-8.01 (9H, m, Ar-H).	115 (CN), 119-160 (Ar-C), 180 & 184 (2C=O).	-
2f	3317 (NH), 2211 (CN), 1697 (C=O) 1568 (C=C), 745 (Cl).	10.3 & 9.9 (2H, 2s, 2NH), 7.0-8.1 (9H, m, Ar-H).		390 (M^+, 20), 392 (M^++2, 8), 117 (100)
2g	3261 (NH), 2219 (CN), 1677 (C=O), 1563 (C=C), 1136, 1363 (SO_2-N).	12.5 & 10.7 (2H, 2s, 2NH), 7.0-8.01 (10H, m, Ar-H).	115 (CN), 118-162 (Ar-C), 164 & 186 (C=O).	-
2h	3317(NH), 2212(CN), 1697(C=O), 1567(C=C), 1176, 1366 (SO_2-N), 745(Br).	10.1 & 9.9 (2H, 2s, 2NH), 7.1-8.2 (10H, m, Ar-H).	114 (CN), 118-161 (Ar-C), 162&165 (2C=O).	470(M^+, 8), 472 (M^++2, 1), 157 (100)
3b	3113 (NH), 2216 (CN), 1681 (C=O), 1572 (C=C), 1254 (C=S).	13.17 &12.62 (2H, 2s, 2NH), 8.59 (1H, s, H-2 indole), 7.30-8.0 (4H, m, Ar-H), 4.31 (2H, q, CH_2), 1.41 (3H, t, CH_3).		-
3c	3102 & 3030 (NH), 2219 (CN), 1671 (C=O), 1566 (C=C), 1275 (C=S).	13.2 & 9.93 (2H, 2s, 2NH), 8.72 (1H, s, H-2 indole), 7.34-8.69 (4H, m, Ar-H) of indole, 7.30 (5H, s, Ar-H of phenyl), 5.65 (2H, s, CH_2-N).	56 (CH_2-N), 113 (CN), 118-162 (Ar-C), 180 (C=O), 186 (C=S).	358 (M^+, 12), 91 (100)
3d	3281& 3124 (NH), 2218 (CN), 1696 & 1710 (C=O), 1566 (C=C), 1267 (C=S).	10.3 & 9.3 (2H, 2s, 2NH), 7.01-8.1 (10H, m, Ar-H).	115 (CN), 118-156 (Ar-C), 180 (C=O), 186 (C=S).	372(M^+, 25), 139 (100)
3e	3167 & 3104 (NH), 2220(CN), 1699 (C=O), 1568 (C=C), 1238 (C=S), 757 (Cl).	10.1 & 9.9 (2H, s, 2NH), 7.01-8.01 (9H, m, Ar).	115 (CN), 118-1155 (Ar-C), 180 (C=O), 184(C=S).	-
3f	3320 (br, NH), 2213 (CN), 1695 (C=O), 1568 (C=C), 1264 (C=S), 749 (Cl).	12.2 &10.1 (2H, 2s, 2NH), 7.2-8.4 (9H, m, Ar-H).	117 (CN), 118-161 (Ar-C), 167 & 172 (C=O), 184 (C=S).	406 (M^+, 8), 408 (M^++2, 2), 240 (100)
3g	3316 (br, NH), 2211 (CN), 1777, 1695 (C=O), 1570 (C=C), 1363& 1134 (SO_2-N), 1259 (C=S).	10.2 & 9.9 (2H, 2s, 2NH), 7.01-8.01 (10H, m, Ar-H).	115 (CN), 118-160 (Ar-C), 164 (C=O), 172 (C=S).	-
3h	3447, 3111 (NH), 2218 (CN), 1679 (C=O), 1576 (C=C), 1342 & 1122 (SO_2-N), 1258 (C=S), 745 (Br).	10.1 & 9.3 (2H, 2s, 2NH), 7.01-8.2 (9H, m, Ar-H).		486(M^+, 8), 488 (M^++2, 7), 240 (100)

Table II: cont.

Compd. No.	IR (ν_{max} cm^{-1})	NMR (δ, ppm)		MS (*m/z*, %)
		^1H	^{13}C	
4b	2211 (CN), 1569 (C=C).	8.6 (1H, s, H-2 indole), 8.5 (1H, s, CH=C), 7.34-8.0 (4H, m, Ar-H) of indole, 4.33 (2H, q, CH_2), 1.41 (3H, t, CH_3).		
4e	2217 (CN), 1661 (C=O), 1565 (C=C), 739 (Cl).	8.7 (1H, s, H-2 indole), 8.52 (1H, s, CH=C), 7.28-8.05 (8H, m, Ar-H).		
4f	2216 (CN), 1678 (C=O), 1565 (C=C), 739 (Cl).			
4g	2216 (CN), 1595 (C=C), 1350 & 1140 (SO_2-N).			
4h	2216 (CN), 1570 (C=C), 1348 &1144 (SO_2-N), 750 (Br).			
5a	3279 (NH_2), 3160 (NH of indole), 2219 (CN), 1612 (C=N), 1568 (C=C).	12.7 (1H, s, NH), 8.7 (2H, s, NH_2), 8.5 (1H, s, H-2 indole), 7.3-8.0 (8H, m, Ar-H).	69 (C-CN), 115 (CN), 110, 113, 119-136 (Ar-C), 152 (C=N).	324 (M^+, 8), 116 (100)
5b	3432 (NH_2), 2211 (CN), 1569 (C=N), 1512 (C=C).	8.68 (2H, s, NH_2), 8.50 (1H, s, H-2 indole), 7.3-8.0 (8H, m, Ar-H), 4.33 (2H, q, CH_2), 1.41 (3H, t, CH_3).	14.95 (CH_3), 42 (CH_2), 68 (C-CN), 115 (CN), 110, 111, 119, 122-135 (Ar-C), 151 (C=N).	-
5c	3428 (NH_2), 2214 (CN), 1585 (C=N), 1511 (C=C).	8.7 (1H, s, H-2 indole), 7.2-7.6 (13H, m, Ar-H), 5.7 (2H, s, CH_2), 4.0 (2H, s, NH_2).	50 (CH_2-N), 69 (C-CN), 115.7 (CN), 110,111,119,122-136 (Ar-C), 151(C=N).	414 (M^+, 35), 242 (100)
5d	3280 (NH_2), 2218 (CN), 1698 (C=O), 1616 (C=N), 1567 (C=C).	7.01-8.1(14H, m, Ar-H), 6.1 (2H, s, NH_2).	115 (CN), 118-156 (Ar-C), 158 (C-NH_2), 166 (C=N).	-
5e	3278 (NH_2), 2215 (CN), 1680 (C=O), 1616 (C=N), 1566 (C=C), 739 (Cl).	8.7 (2H, s, NH_2), 8.5 (1H, s, H-2 indole), 7.2-8.05 (8H, m, Ar-H),	115 (CN), 119-152 (Ar-C), 162 (C=N), 168 (C-NH_2).	462 (M^+, 10), 464 (M^++2, 8), 193 (100)
5f	3278 (NH_2), 2216 (CN), 1690 (C=O), 1621 (C=N), 1565 (C=C), 737 (Cl).	7.01-8.1 (13H, m, Ar-H), 4.2 (2H, s, NH_2).		-
5g	3369 (NH_2), 2184 (CN), 1631 (C=N), 1563 (C=C), 1370 & 1175 (SO_2-N).	9.9 (2H, s, NH_2), 8.7 (1H, s,H-2 indole), 7.01-8.2 (13H, m, Ar-H).	114 (CN), 118-138 (Ar-C), 161-166 (C=N), 180 (C-NH_2)	-
5h	3420 (NH_2), 2216 (CN), 1616 (C=N), 1590 (C=C), 1361 &1185 (SO_2-N), 738 (Br).	8.5 (1H, s, H-2 indole), 7.1-7.88 (12H, m, Ar-H), 6.1 (2H, s, NH_2).	117 (CN), 118-141 (Ar-C), 161 & 180 (C=N), 185 (C-NH_2).	544 (M^+, 7), 546 (M^++2, 7), 193 (100)

Table III: Anti-inflammatory activity of the most active

Compd. No.	Dose (mg kg^{-1})	Inhibition (%)
control	0	0
flufenamic acid	20	53
indomethacin	5	51
2a	20	45
	5	19
2e	20	62
	5	24
2f	20	69
	5	45
2h	20	69
	5	65
3a	20	62
	5	19
3e	20	62
	5	57
3f	20	84
	5	54
3h	20	65
	5	57
5a	20	24
	5	19
5e	20	57
	5	24
5f	20	62
	5	54
5h	20	24
	5	19

Significant difference from the control value at $p< 0.05$

Table IV: Analgesic activity of most active compounds

Compd. No.	Dose (mg kg^{-1})	Protection (%)
control	0	0
indomethacin	5	63
flufenamic acid	20	66
2a	50	66
	25	33
2f	50	100
	25	50
3a	50	50
	25	33
3e	50	100
	25	33
3f	50	100
	25	50
3h	50	66
	25	33
5e	50	83
	25	66
5f	50	83
	25	50

Table V: Anticonvulsant activity of the new prepared compounds

Compd. No.	Dose (mg kg^{-1})	Protection (%)	Compd. No.	Dose (mg kg^{-1})	Protection (%)
control	0	0	**control**	0	0
diazepam	5	50	**diazepam**	5	50
2a	25	50	**3e**	25	83
	12.5	16		12.5	50
2b	25	33	**3f**	25	83
	12.5	16		12.5	66
2c	25	33	**3g**	25	50
	12.5	16		12.5	16
2d	25	33	**3h**	25	33
	12.5	16		12.5	33
2e	25	50	**5a**	25	33
	12.5	33		12.5	16
2f	25	66	**5b**	25	33
	12.5	33		12.5	16
2g	25	33	**5c**	25	33
	12.5	16		12.5	16
2h	25	50	**5d**	25	33
	12.5	33		12.5	16
3a	25	50	**5e**	25	50
	12.5	16		12.5	33
3b	25	33	**5f**	25	50
	12.5	16		12.5	33
3c	25	33	**5g**	25	50
	12.5	16		12.5	33
3d	25	33	**5h**	25	16
	12.5	16		12.5	0

Table (VI): Antimicrobial potential of the new synthesized compounds

Compd. No	Inhibition Zone (mm)														
	E. coli			*P. aeruginosa*			*S. aureus*			*B. cereus*			*C.albicans*		
	100µg	50µg	25µg	100µg	50µg	25µg	100µg	50µg	25µg	100µg	50µg	25µg	100µg	50µg	25µg
2b	15	10	-	15	10	-	10	-	-	10	-	-	12	-	-
2c	14	10	-	14	10	-	10	-	-	10	-	-	12	-	-
2d	13	10	-	15	10	-	10	-	-	10	-	-	10	-	-
2e	16	10	-	15	10	-	12	-	-	10	-	-	10	-	-
2f	18	10	-	16	10	-	13	-	-	10	-	-	10	-	-
2g	18	10	-	17	10	-	10	-	-	10	-	-	12	-	-
2h	18	10	-	17	10	-	14	-	-	10	-	-	12	-	-
3b	17	10	-	16	10	-	12	-	-	8	-	-	10	-	-
3c	18	10	-	18	10	-	12	-	-	8	-	-	10	-	-
3d	18	11	-	18	10	-	13	-	-	9	-	-	10	-	-
3e	19	11	-	18	10	-	12	-	-	9	-	-	10	-	-
3f	19	12	-	17	10	-	10	-	-	8	-	-	12	-	-
3g	19	10	-	17	10	-	10	-	-	7	-	-	12	-	-
3h	19	10	-	17	10	-	10	-	-	8	-	-	11	-	-
5a	13	10	-	12	10	-	10	-	-	10	-	-	11	-	-
5b	12	10	-	12	-	-	11	-	-	9	-	-	11	-	-
5c	12	10	-	11	-	-	10	-	-	8	-	-	10	-	-
5d	13	10	-	11	-	-	9	-	-	10	-	-	9	-	-
5e	12	10	-	10	-	-	8	-	-	8	-	-	8	-	-
5f	12	10	-	10	-	-	8	-	-	9	-	-	8	-	-
5g	12	10	-	10	-	-	8	-	-	9	-	-	8	-	-
5h	12	10	-	10	-	-	8	-	-	9	-	-	8	-	-
Cefatoxime	22	20	19	19	19	15	22	20	17	22	20	15	-	-	-
Piperacillin	-	-	-	18	17	12	22	20	15	17	15	12	-	-	-
Nystatin (30 unit)	-	-	-	-	-	-	-	-	-	-	-	-	23		