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Pharmacological Screening of 6H, 11H-Indolo [3, 2-c] isoquinolin-5-ones and their Derivatives#

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Fifteen different indolo[3, 2-c]isoquinolin-5-ones and their derivatives prepared earlier were screened for analgesic, antiinflammatory, oxytocic, anthelmintic and antimicrobial activities. Compounds 1a,2a, 3a-b, 4a and 6c exhibited promising analgesic activity while compounds 1b and 2a-c showed maximum anti-inflammatory activity. The only compound that showed maximum anthelmintic activity is 3b. The compound 2b exhibited promising antibacterial activity against all the organisms tested. Whereas, compounds 1b, 3b and 5b showed high activity against *E.coli*. Antifungal activity revealed that compounds 5b and 5c were active against *C. albicans*, whereas, compounds 1c and 2b were found to be active against *A. niger*.

LITERATURE survey revealed that the nitrogen heterocycles have gained importance on account of their various types of pharmacological properties. Indoloisoquinolines are also known for their variety of biological and pharmacological properties such as, antibacterial[1,2], anticancer[2,3] and antihistamine[4] activities. The pyrazole, oxadiazole-2-thione and pyrazolone systems are also known for their broad pharmacological profile[5-7].

Therefore, in continuation of our work on potent indoloisoquinoline derivaties[8-10] and in view of the importance of indoloisoquinoline, pyrazole, pyrazolone and oxadiazole-2-thione systems, it has been considered appropriate to screen the title compounds for their possible pharmacological properties, since the synthesis and structural characterization are reported previously from our laboratory[8].

MATERIALS AND METHODS

Analgesic Activity : Tail flick method[11] was adopted for the evaluation of analgesic activity. Albino mice of either sex weighing between 20-25 g were randomly distributed in control, standard and test (four animals each) groups. The test compounds were administered orally at a dose of 30 mg/kg. The standard group was administered analgin at a dose of 50 mg/kg, orally. The reaction time was noted at 0, 15, 30 and 60 min after the drug administration. Percent protection against tail flicking was calculated using the following formula, % protection=(1-wt/wc)100, where wt and wc are the means of the tail flicking in the test and control, respectively. The results are recorded in Table-1.

Anti-Inflammatory Activity

This study was evaluated by formalin-induced rat hind paw odema method[11]. Albino rats of either sex weighing between 150-200 g were distributed into control, standard and test (four animals each) groups. At zero hour, the test compounds and phenylbutazone were administered orally at a dose of 30 mg/kg, and 100 mg/kg respectively. After 30 min of treatment, an inflammatory odema was induced in the hind paw by injection of 0.1 ml of formalin (1% w/v) into the plantar tissue of the paw. The initial volume of the paw was measured plethysmographically within 30 sec of the injection. The relative increase in the paw volumes after 4 h of the formalin injection was noted. The percent inhibition of the inflammation was calculated by the

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Table-1 : Analgesic Activity of 6H, 11H-Indolo-[3,2-c] isoquinolin-5-ones and their derivatives.

Sl. No.	Compound	Dose (mg/kg)	time taken to remove the tail at different time interval. (mean±S.E.M. Sec) 0 min	15 min	30 min	60 min
1.	Control (Tween-80)	-	3.30 (±0.024)	3.20 (±0.007)	3.10 (±0.030)	3.50 (±0.089)
2.	Standard (Analgin)	50	4.43 (±0.008)	5.33 (±0.046)	5.96 (±0.045)	6.10 (±0.158)
3.	1a	30	3.30 (±0.034)	3.87 (±0.064)	7.17 (±0.009)	7.45 (±0.063)
4.	1b	30	4.70 (±0.113)	5.20 (±0.060)	6.20 (±0.006)	4.45 (±0.546)
5.	1c	30	3.37 (±0.069)	4.30 (±0.008)	7.25 (±0.026)	5.12 (±0.022)
6.	2a	30	4.75 (±0.083)	5.15 (±0.003)	7.65 (±0.056)	6.25 (±0.036)
7.	2b	30	3.90 (±0.006)	5.30 (±0.046)	7.45 (±0.016)	3.65 (±0.016)
8.	3a	30	3.50 (±0.045)	7.60 (±0.020)	6.25 (±0.022)	3.17 (±0.064)
9.	3b	30	3.20 (±0.006)	7.22 (±0.002)	7.52 (±0.002)	3.80 (±0.006)
10.	3c	30	3.10 (±0.006)	3.50 (±0.020)	6.60 (±0.186)	4.75 (±0.010)
11.	4a	30	3.50 (±0.020)	4.50 (±0.020)	8.62 (±0.089)	5.27 (±0.029)
12.	4b	30	4.65 (±0.083)	5.80 (±0.180)	5.90 (±0.153)	6.42 (±0.155)
13.	6c	30	4.50 (±0.180)	7.07 (±0.009)	7.37 (±0.009)	8.65 (±0.836)

Each group consisted of 4 animals.

formula,, % inhibition = (1-vt/vc) 100, where vt and vc are the mean relative changes in the paw volume of the test and control, respectively. The results are summarised in the Table-2.

Anthelmintic Activity

Was evaluated on *Pherituma posthuma* by following the reported method[12]. The organisms *Pherituma posthuma* were washed with normal saline to remove the adhering material. The compounds were tested at a dose of 2 mg/ml suspension in 0.1% Tween-80 solution in saline. Mebendazole was used as a standard at dose of 2 mg/ml suspension in 0.1% Tween-80 solution in saline. Petridishes of nearly equal size were taken and 20 ml of normal saline, Tween-80 solution and mebendazole suspension were

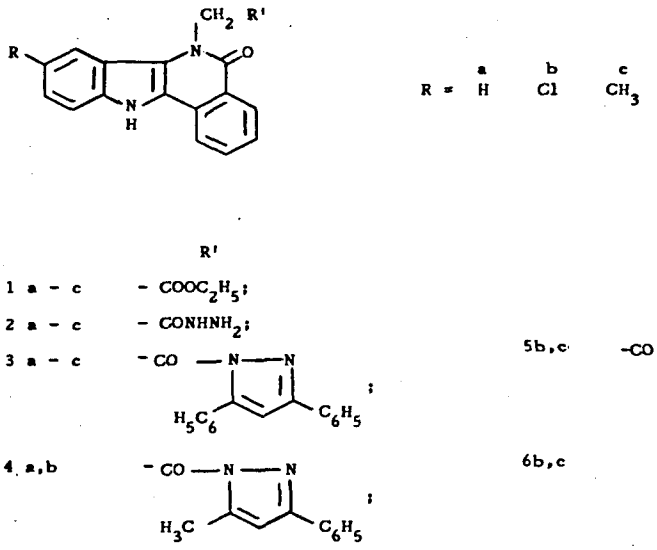

Table-2 : Antiinflammatory Activity of test compounds

Sl. No.	Group	Dose (mg/kg)	oedema at 4h mean±S.E.M.
1.	Control (Tween-80)	—	0.230 (±0.061)
2.	Standard (Phenyl butazone)	100	0.130 (±0.080)
3.	1a	30	0.480 (±0.013)
4.	1b	30	0.305 (±0.193)
5.	2a	30	0.405 (±0.002)
6.	2b	30	0.435 (±0.000)
7.	2c	30	0.377 (±0.012)
8.	3c	30	0.437 (±0.002)

Each group consisted of 4 animals.

poured into separate petridishes as a control, blank and standard, respectively. Twenty ml of test compound suspension were taken in different petridishes. The time taken for complete death of worms was noted. The time taken by worm to become motionless was noted as paralysis time. Number of observations were made to confirm the readings.

Antimicrobial Activity

The *in vitro* antimicrobial activity was carried out against 24 h cultures of four selected bacteria and two fungi. The bacteria used were *S. Citrus, P. aeruginosa, P.vulgaris* and *E. coli* and the fungi used were *C. albicans* and *A. niger.*

The antimicrobial activity was performed by cup-plate method[13]. Nutrient agar and potato dextrose agar were used to culture the bacteria and fungi, respectively. the compounds were tested at a concentration of 50 µg/ml and 75 µg/ml in DMF solution, for bacteria and fungi, respectively. The solution of gentamycin (40 µg/ml) and

Table-3 : *In vitro* Antimicrobial Activity of the Test Compounds

Sl. No.	Compound	Diameter of zone of inhibition in mm*					
		S.citreus	*P.aeruginosa*	*P.vulgaris*	*E.coli*	*C.albicans*	*A.niger*
1.	1b	08	10	16	18	10	15
2.	1c	10	14	09	08	17	21
3.	2b	17	17	18	17	11	22
4.	3b	08	09	12	18	13	18
5.	4b	11	14	18	14	10	09
6.	5b	14	08	08	16	23	15
7.	5c	09	15	14	08	22	10
8.	Gentamycin	20	21	20	19	-	-
9.	Griseofulvin	-	-	-	-	25	28

* Including diameter of the well
Control (DMF) = No activity
Antibacterial - Gentamycin 40 μg/ml; Test compound dose-50 μg/ml
Antifungal - Griseofulvin- Griseofulvin - 20 μg/ml ; Test compound dose 75 μg/ml

griseofulvin (20 μg/ml) were prepared in sterile water and used as standards for comparison of antibacterial and antifungal activity, respectively. The plates were inoculated with 24 h culture of respective bacteria and fungi, with the help of a sterile cork borer (8 mm), cups were cut out and into each of these cups 0.1 ml of each of the test solution and the control (DMF) were placed separately under aseptic conditions with the help of sterile syringes. The plates were then maintained at room temperature for 2 h to allow the diffusion of the solution into the medium and incubated at 37±0.5° for bacteria and at room temperature for fungi, respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria and 48 h for fungi. Each experiment was repeated thrice and the average of three independent determination were recorded. The results are summarised in the Table-3.

Suspensions of the test compounds were prepared in 0.1% v/v Tween-80 solution. In all the cases, the control received the same quantity of Tween-80 solution. Standard errors were computed by usual methods.

RESULTS AND DISCUSSION

Analgesic activity study reveals that the compounds **1a, 2a, 3a-b, 4a** and **6c** were found to be active, while, moderate activity was exhibited by the compounds **1b-c, 2b, 3c** and **4b** and the rest of the compounds were inactive. Statistically it was found that there was no reduction in the oedema in all the groups administered with test drug after 1 h. After 4 h, there was promising reduction in oedema in the groups administered with the test drugs **1b, 2a** and **2c,** where as, in case of compounds **1a, 2b** and **3c** there was moderate reduction in oedema. The remaining compounds were found to be inactive.

When anthelmintic activity on *Pherituma posthuma* was carried out, only compound **3b** showed anthelmintic activity, whereas, the rest of the compounds were either moderately active or inactive. Antibacterial activity investigation revealed that, compound **2b** showed promising activity against all the four organisms. Whereas, compound 4b exhibited maximum activity against *P. vulgaris* and compounds 1b, 3b, and 5b showed high activity against *E. coli.* Determination of a antifungal activity showed that,

compounds **5b** and **5c** were active against *C. albicans,* whereas, compound **1c** and **2c** were active against *A. niger.*

The above *in vivo* and *in vitro* experimental results indicated that test compound (6H, 11H-indolo[3,2-c]isoquinolin-5-one-6-yl) acetyl hydrazide (2a) exhibited promising analgesic and antiinflammatory activities. Ethyl-(8-chloro-6H, 11H-indolo-[3, 2-c]isoquinolin-5-one-6-yl) acetate (**1b**) showed maximum antiinflammatory activity and moderate analgesic activity. Compound 1-(8-chloro-6H, 11H-indolo[3,2-c]isoquinolin-5-one-6-yl)acetyl-3,5-diphenylpyrazole (**3b**) has been found to be the most potent anthelmintic. It also showed promising antibacterial activity against *E. coli.* Compound (8-chloro-6H, 11H-indolo-[3,2-c]isoquinolin-5-one-6-yl) acetyl hydrazide (**2b**) exhibited maximum zone of inhibition against all the four bacteria tested and against *A. niger.* It also revealed moderate antiinflammatory and analgesic activities. From the above discussion it can be concluded that compound **2b** was found to be most potent in all the activities performed. This may be due to the active hydrazide groups in the molecule.

REFERENCES

1. Winter, G., Dimola, N., Berti, M., and Ariali, V., **Farmaco Ed. Sci.,** 1979, 34, 507.
2. Ishizumi, K. and Katsube, J., **British Pat.** 2, 025, 932, 1980; **Chem. Abstr.,** 1980 93,186, 322e.
3. Sumifomo Chemical Co. Ltd. **Japan KokaiTokyo Koho. Jap. Pat.,** 1983, 5869,882; **Chem Abstr.,** 1983, 99, 88182P.
4. Kosuge, T., Zend, H. and Torigoe, J., **Japan Kokai., Jap. Pat.,** 1973, 7391, 210; **Chem. Abstr.,** 1974, 80, 112616.
5. Aderson, E.L., Cosely, J.E., Green Jr., L.C., Lafferty., J.L. and Reiff, H.E., **J. Med. Chem.,** 1964, 7, 259.
6. Okamoto, T., Trikura, T., Suzue, S., Ushiyama, K., Matsui, Y., Magatsu, Y., Sato S., Yakyama, H. and Saito, **Jap. Pat.,** 1983, 7372, 193; Chem. Abstr., 1984, 80, 37015r.
7. Schweiss, D. and Nordon, J.C. **US Pat.,** 1982, 4, 346, 97; **Chem. Abstr.,** 1982, 97, 216193.
8. Hiremath, S.P., Saundane, A.R. and Mruthyunjaya swamy, B.H.M., **J. Heterocylic Chem.** 1993, 30, 603.
9. Hiremath, S.P., Saundane, A.R., Swamy, H.K.S. and Mruthyunjayaswamy, B.H.M., **Indian J. Heterocyclic Chem.,** 1993, 30, 37.
10. Hiremath, S.P., Saundane, A.R. and Mruthyunjayaswamy, B.H.M., **J. Indian Chem., Soc.,** 1995, 72, 735.
11. Kulkarni, S.K. In "Hand book of Experimental pharmacology" Ist Ed., Vallabh Prakashan, Delhi, 1987, 63, 65.
12. Giand, K.N., Dar, R.N., Chopra, B.M. and Kaul, R.N., **Indian J. Pharm.,** 1965, 27, 141.
13. **"Indian Pharmacopoeia",** Government of India, 3rd Ed., New Delhi, 1985, Apendix IV, 90.