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SEARCH FOR NEW DRUGS

R-BENZYLIDENEHYDRAZIDES OF NH-FUROYL-5-IODOANTHRANILIC ACIDS: SYNTHESIS, PROPERTIES, AND ANALGESIC AND ANTIBACTERIAL ACTIVITY

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A series of R-benzylidenehydrazides of NH-furoyl-5-iodoanthranilic acid were synthesized by condensing NH-furoyl-5-iodoanthranilic acid hydrazide with aromatic aldehydes. Their structures were confirmed using IR and PMR spectroscopy. Their analgesic and antibacterial activities were studied.

Keywords: 5-iodoanthranilic acid derivatives, synthesis, analgesic and antibacterial activity.

New drugs are currently designed using strategies varying from investigations of biologically active herbal and animal compounds to screening protocols and chemical modification of known drugs. Modification consists essentially of altering the chemical structure of a known drug to produce a more active new drug. Examples of the latter are derivatives of anthranilic acid that are used as drugs with analgesic, anti-inflammatory, hypoglycemic, and other types of biological activity and low toxicity [1].

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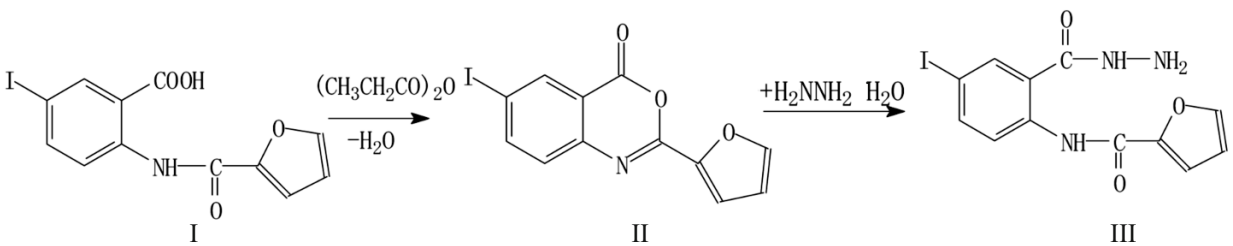
The goals of the work were to synthesize substituted hydrazides of NH-furoyl-5-iodoanthranilic acid and to study their antimicrobial and analgesic activity.

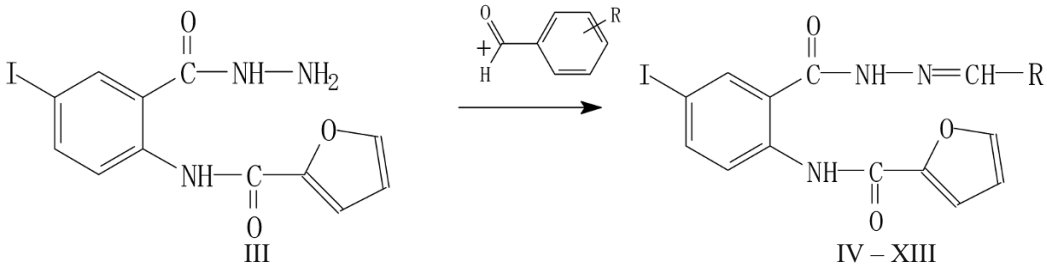
The starting material was NH-furoyl-5-iodoanthranilic acid (**I**), intramolecular cyclization of which in propionic anhydride produced 2-furoyl-6-iodo-3,1-benzoxazin-4-one (**II**). Compound **II** in EtOH was stirred with hydrazine hydrate for 1 h at 18 – 20°C to synthesize NH-furoyl-5-iodoanthranilic acid hydrazide (**III**) (Scheme 1) as before [2]. Then, **III** was condensed with aromatic aldehydes at 18 – 20°C in EtOH in the presence of a catalytic amount of conc. HCl to afford the corresponding R-benzylidenehydrazides of NH-furoyl-5-iodoanthranilic acid (**IV**-**XIII**) (Scheme 2).

The synthesized compounds were crystalline or amorphous; white or white with a yellow, green, or pink tint; in-

Scheme 1



Scheme 2



III IV – XIII

R = -C_6H_5 (IV); R = 2-OH,5-$NO_2C_6H_3$ (V); R = 2-hydroxynaphthyl (VI); R = 4-$N(C_2H_5)_2C_6H_4$ (VII); R = 4-ClC_6H_4 (VIII); R = 4-$N(CH_3)_2C_6H_4$ (IX); R = 2,4-$(OCH_3)_2C_6H_3$ (X); R = 4-IC_6H_4 (XI); R = 4-$NO_2C_6H_4$ (XII); R = 2-NO_2 C_6H_4 (XIII).

soluble in H_2O and EtOH; and soluble in organic solvents (DMSO, DMF). Their structures were elucidated using PMR and IR spectroscopy.

PMR spectra of **IV** – **XIII** exhibited resonances for aromatic protons as multiplets at 6.59 – 9.37; hydrazide protons as singlets at 11.57 – 11.99; and amide protons as singlets at 11.82 – 12.47 ppm.

IR spectra of **IV** – **XIII** contained bands for amide stretching vibrations at 3240 – 3192; hydrazide carbonyl, 1680-1660; amide carbonyl, 1640 – 1620; and azomethine, 1600-1590 cm^{-1}.

Table 1 lists the physicochemical and spectral characteristics of **IV** – **XIII**.

EXPERIMENTAL CHEMICAL PART

PMR spectra were recorded in DMSO-d_6 with TMS internal standard on Bruker AM-300 (300 MHz) and AM-400 instruments (400 MHz). IR spectra were taken from KBr pellets on a Specord M-80 instrument. The purity of products was monitored using TLC with elution by C_6H_6—$CHCl_3$—Me_2CO (9:1:1) and detection by I_2 vapor. TLC used Sorbfil PTSKh-P-V plates (TU 26-11-17–89). The obtained R_f values spanned the range 0.3 – 0.7. Tests results were considered positive if a single spot was observed in the chromatogram.

Hydrazide of NH-furoyl-5-iodoanthranilic acid (III). A solution of **II** (0.3 g, 0.00088 mol) in EtOH (5 mL) was treated with hydrazine hydrate (0.06 mL, 0.0013 mol). The mixture was stirred for 1 h at 18-20°C. The resulting product was filtered off, dried, and recrystallized from EtOH:MeCN (1:1). Yield 0.26 g (79.7%); mp = 224 – 226°C. PMR spectrum (DMSO-d_6, δ, ppm): 6.62 – 8.34 m (8H, Ar + NH_2); 12.53 sec (1H, NHCO).

2-Hydroxy-5-nitrobenzylidenehydrazide of NH-furoyl-5-iodoanthranilic acid (IV). Compound **III** (0.3 g, 0.0134 mol) was dissolved in EtOH (5 mL), treated with conc. HCl (one drop) and 2-hydroxy-5-nitrobenzylidenehydrazide (0.4 g, 0.0038 mol), held for 1 h at 18 – 20°C, neutralized with $NaHCO_3$ solution to pH 5, filtered, dried,

TABLE 1. Physicochemical and Spectral Characteristics of **IV** – **XIII**

Compound	Empirical formula	mp, °C	Yield, %	PMR ^{1}H, δ, ppm
IV	$C_{19}H_{14}IN_3O_3$	236 – 238	44.5	6.67 – 8.37 m (12H, 3Ar + CH); 11.69 s (H, CONH); 12.00 s (H, NHCO)
V	$C_{19}H_{15}IN_4O_6$	245 – 247	78.5	3.08 s (1H, OH); 6.71 – 8.84 m (10 H, 3Ar + CH); 11.99 s (H, CONH); 12.47 s (H, NHCO)
VI	$C_{23}H_{16}IN_3O_4$	264 – 266	81.3	6.67 – 9.37 m (13H, 4Ar + CH); 11.72 s (H, CONH); 12.00 s (H, NHCO)
VII	$C_{23}H_{23}IN_4O_3$	138 – 140	73.5	0.99 – 1.17 t (6H, $2CH_3$); 3.29 – 3.46 m (4H, $2CH_2$); 6.63 – 8.31 m (11H, 3Ar + CH); 11.70 s (H, CONH); 11.83 s (H, NHCO)
VIII	$C_{19}H_{13}ClIN_3O_3$	236 – 237	52.7	6.75 – 8.71 m (11H, 3Ar + CH); 11.79 s (H, CONH); 12.23 s (H, NHCO)
IX	$C_{21}H_{19}IN_4O_3$	196 – 198	46.7	3.29 s (6H, CH_3); 6.67 – 8.32 m (11H, 3Ar + CH); 11.73 s (H, CONH); 11.82 s (H, NHCO)
X	$C_{21}H_{18}IN_3O_5$	228 – 229	89.0	3.83 s (6H, $2OCH_3$); 6.59 – 8.63 m (10H, 3Ar + CH); 11.85 s (H, CONH); 12.15 s (H, NHCO)
XI	$C_{19}H_{13}I_2N_3O_3$	256 – 257	46.5	6.70 – 8.39 m (11H, 3Ar + CH); 11.69 s (H, CONH); 12.00 s (H, NHCO)
XII	$C_{19}H_{13}IN_4O_5$	230 – 232	59.8	6.72 – 8.27 m (11H, 3Ar + CH); 11.57 s (H, CONH); 12.22 s (H, NHCO)
XIII	$C_{19}H_{13}IN_4O_5$	258 – 260	47.3	6.70 – 8.90 m (11H, 3Ar + CH); 11.76 s (H, CONH); 12.31 s (H, NHCO)

and recrystallized from EtOH:MeCN (1:1). Compounds **V** – **XIII** were prepared analogously.

EXPERIMENTAL BIOLOGICAL PART

The analgesic and antibacterial activities of R-benzylidenehydrazide NH-furoyl-5-iodoanthranilic acids **III** – **XIII** were studied.

The analgesic activity of **III** – **XIII** was determined using white mice of both sexes (22 – 24 g) and the hot-plate thermal irritation method [3]. Tested compounds were injected i.p. at a dose of 50 mg/kg as suspensions in 2% starch solution 30 min before placing animals on a metal plate heated to 53.5°C. The residence time (measured in seconds) on the hot plate before manifestation of a behavioral response to a nociceptive stimulus (licking hind paws, jumping, withdrawing hind paws) served as the pain sensitivity parameter. Effects were evaluated 0.5, 1.0, and 2.0 sec after injecting the compounds. Each compound was tested in six animals. Results were assessed from the increased time for onset of a defensive reflex as compared with the initial data. Control animals were injected with starch solution (2%). The reference drug was commercially available metamizole sodium (OOO Farmkomplekt). The compounds were tested at doses of 3 – 6 – 12 and 5 – 25 – 50 mg/kg of animal body mass as recommended in the *Handbook for Experimental (Preclinical) Studies of New Drugs* [4]. Our compounds were tested at a dose of 50 mg/kg, which was close to the dose of reference drug metamizole sodium (93 mg/kg) corresponding to ED_{50} for the hot-plate test, because they were marginally toxic according to the Sidorov classification [5].

TABLE 2. Analgesic Activity of **III** – **XIII**

Compound	Onset time of defensive reflex, s
III	20.58 ± 0.18*
IV	24.80 ± 1.28*
V	20.32 ± 1.22*
VI	23.20 ± 0.72*
VII	19.10 ± 0.44*
VIII	19.60 ± 0.40*
IX	20.10 ± 0.68*
X	22.32 ± 0.55*
XI	19.44 ± 0.64*
XII	23.38 ± 1.16*
XIII	26.72 ± 1.22*
Control	10.30 ± 0.60
Metamizole sodium	16.33 ± 3.02 ($p < 0.1$)

* Statistically significant differences vs. control ($p < 0.05$); metamizole sodium ($p < 0.1$).

Experimental results were processed statistically using the Student *t* criterion [6]. Effects were considered statistically significant for $p \le 0.05$. Table 2 presents the pharmacological test results.

The analgesic activities of the tested compounds were found to be more pronounced than that of metamizole sodium. The most active compounds were **IV** (R = $–C_6H_5$), **VI** (R = 2-hydroxynaphthyl), **VIII** (R = 4-ClC_6H_4), **XII** (R = 4-$NO_2C_6H_4$), and **XIII** (R = 2-$NO_2C_6H_4$), for which the onset time of the defensive reflex was 24.80, 23.32, 23.20, 26.72, and 23.38 sec, respectively.

The antibacterial activities of the synthesized compounds against standard strains *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 6538P using double serial dilutions in meat-peptone broth with bacterial loading 250,000 microbial units per mL of solution [3]. The active dose was the minimum inhibitory concentration (MIC) of the compounds, i.e., the minimal dilution leading to complete suppression of bacterial test culture development. The bacteriostatic effects of the tested compounds were compared with those of furacilin and chloramine B. Table 3 presents the test results.

Compound **V** was four times more active than furacilin and eight times more active than chloramine B against *S. aureus*. Compound **VI** was about as active as chloramine B against *S. aureus*. The other compounds exhibited weak antibacterial activity against both strains.

The mechanism of analgesic activity, i.e., the effect on the enzyme COG, was proposed primarily as a peripheral effect considering the similarity of the structures of the tested compounds, diclofenac sodium, and acetylsalicylic acid. The mechanism of antibacterial activity (bactericidal or bacteriostatic) of the synthesized compounds was difficult to discern based on the screening studies. This issue will be studied in more detail.

Thus, the biological tests indicated that the search for compounds with analgesic and antibacterial activity among

TABLE 3. Antibacterial Activity of **IV** – **X**

Compound	MIC, μg/kg	
	St. Aureus ATCC6 6538-P	*E. Coli* ATCC 25922
IV	1000	1000
V	62.5	1000
VI	500	1000
VII	1000	1000
VIII	1000	1000
IX	1000	1000
X	1000	1000
Furacilin	250	125
Chloramine B	500	250

R-benzylidenehydrazides of NH-furoyl-5-iodoanthranilic acid is promising.

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