

SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF CERTAIN ESTERS OF ANTHRANILIC ACID CONTAINING THE SULFANILAMIDE MOIETY

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The potassium salts of N-substituted anthranilic acid (I) were allowed to react with N⁴-chloroacetylsulfonamides (II), to give substituted aminosulfamoylphenyl aminocarbonylmethyl, N-substituted anthranilic acid esters (III). The structure of the produced ester (III) were confirmed by microanalytical and spectral data. Preliminary pharmacological testing of the new esters showed that, some derivatives were found to possess marked antipyretic, analgesic and antispasmodic activities compared with paracetamol and atropine as reference drugs.

Key words: Anthranilic acid, Sulfanilamide moiety, Ester

Introduction

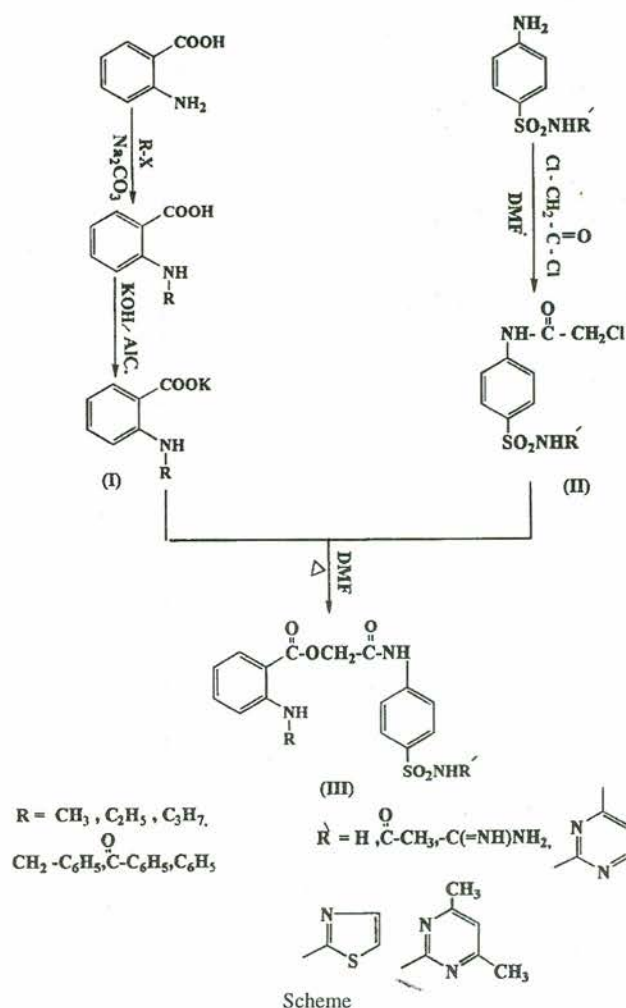
Certain members of N-alkyl, acyl, cyclohexyl, aryl and N-aralkyl anthranilic acid derivatives have been reported to exhibit analgesic, antipyretic, muscle relaxant, antiinflammatory and spasmolytic activities (Fujimura *et al* 1964; Sisodia *et al* 1966; Nakanishi *et al* 1967; Spano and Marri 1968; Fujimura *et al* 1969; SERDEX 1971; Linari and Spano 1971; El-Helby and Abdel Wahab 1995) In many reports of analgesic and antiinflammatory activities, sulfamoyl containing compounds were claimed to posses antiinflammatory action against carrageenin induced inflammation (Mizzoni and Blatter 1971 and 1972; George and Moore 1974).

Consequently, it was decided to synthesize certain new derivatives of substituted aminosulfamoylphenylamino-carbonylmethyl N-substituted anthranilic acid esters (III) aiming to obtain a good analgesic, antipyretic and antispasmodic activities, using the following scheme.

Experimental

Melting points were recorded on a Griffin melting point apparatus and are uncorrected. Micronalyses were performed on Perkin-Elmer CHN analyzer 240 at the Central Laboratory, Faculty of Science, Ain Shams University, IR spectra (KBr) were recorded on a Buck Scientific 500 IR Spectrophotometer and ¹HNMR spectra on a Burker 200 MHz NMR Spectrometer at the Central laboratory, Faculty of Science, Ain Shams University.

N-substituted anthranilic acids (Houben and Brasser 1906; Ullmann and Bader 1907; Hey and Turpene 1954) the potassium salts of N-substituted anthranilic acids (Aloi and Johanna 1921; Harold and Gibson 1924; Jakob *et al* 1942)



and N⁴-chloroacetyl sulfanilamide derivatives (Jacobs *et al* 1991; El-Moghazy 1992) were prepared by their reported procedures.

Substituted amino sulfonylphenylaminocarbonyl methyl N-substituted anthranilic acid ester.

(a) *General procedure:* Equimolar quantities (0.01 mol) of compounds (I) and (II) were mixed in DMF (50 ml) and heated on boiling water bath of 2 h, the reaction mixture was cooled, poured onto H₂O and the precipitated product was filtered, washed several times with H₂O, then air dried and recrystallized from toluene-ethanol (1:1 mixture) to afford the ester (III) (Table 1).

(b) *Pharmacological screening:* The synthesized compound (III) were tested for analgesic and antipyretic activities on intact animals (rats) and antispasmodic activity on isolated rabbit intestine.

(1) *Analgesic effect:* The analgesic effect was determined using the writhing method reported by (Okun *et al* 1965). The analgesic effect of the tested compounds were determined as percentage of protection against writhing effect as shown in (Table 3).

(2) *Antipyretic effect:* The antipyretic effect of the test compounds were evaluated as described by Alpermann

(Alpermann *et al* 1972). The results of the antipyretic test are shown in (Table 4).

(3) *Antispasmodic effect:* Compounds (III) were tested for their spasmolytic effect using isolated rabbit intestine as smooth muscle preparation and atropine (Merk) used as spasmolytic standard drug. The spasmolytic effect of the tested compound were determined by recording their effect on a normal contraction and acetylcholine induced contraction of isolated rabbit intestine using modified Magnus technique (Magnus and Arch 1904). The results of the spasmolytic effect of the tested compounds are shown in Tables (5 and 6).

Results and Discussion

The N-alkyl, aralkyl, acyl and aryl anthranilic acids were prepared and converted into their potassium salts (I) using reported procedures (Houben and Brassler 1906; Ullmann and Bader 1907; Aloj and Johanna 1921; Harold and Gibson 1924; Jokobs *et al* 1942) Mean while sulfonamide derivatives were allowed to react with chloroacetyl chloride to afford the

Table 1
Substituted aminosulfamoylphenylamino carbonylmethyl N-substituted anthranilic acid ester (III)

Comp. (III)	R	R	MP °C	Yield %	Mwt	Molecular formula	Analysis Calcd / Found		
							C%	H%	N%
1	CH ₃	H	240-2	73	363	C ₁₆ H ₁₇ N ₃ O ₅ S	52.89 52.90	4.68 4.80	11.57 11.70
2	CH ₃	-COCH ₃	262-2	80	405	C ₁₈ H ₁₉ N ₃ O ₆ S	52.33 53.50	4.69 4.60	10.37 10.60
3	CH ₃	-C(=NH)NH ₂	280-2	74	405	C ₁₇ H ₁₉ N ₅ O ₅ S	50.37 50.70	4.69 4.70	17.28 17.00
4	CH ₃	2-pyrimidinyl	320-22	6	441	C ₂₀ H ₁₉ N ₅ O ₅ S	54.42 54.60	4.30 4.60	15.87 16.00
5	CH ₃	2-thiazolyl	310-12	65	446	C ₁₉ H ₁₈ N ₄ O ₅ S ₂	51.12 51.00	4.03 4.00	12.56 12.70
6	CH ₃	4,6-dimethyl 2-pyrimidinyl	340	60	469	C ₂₂ H ₂₃ N ₅ O ₅ S	56.29 56.00	4.90 5.00	14.92 15.00
7	C ₂ H ₅	H	246	75	377	C ₁₇ H ₁₉ N ₃ O ₅ S	54.11 54.30	5.04 5.00	11.14 11.40
8	C ₂ H ₅	-CO-CH ₃	271	80	419	C ₁₉ H ₂₁ N ₃ O ₆ S	54.42 54.0	5.01 5.00	10.02 10.00
9	C ₂ H ₅	-C(=NH)NH ₂	275	65	419	C ₁₈ H ₂₁ N ₅ O ₅ S	51.55 51.50	5.01 5.00	16.70 16.50
10	C ₂ H ₅	2-pyrimidinyl	300-2	70	455	C ₂₁ H ₂₁ N ₅ O ₅ S	55.38 55.20	4.62 4.50	15.38 15.20
11	C ₂ H ₅	2-thiazolyl	298-300	60	460	C ₂₀ H ₂₀ N ₄ O ₄ S ₂	52.17 52.30	4.35 4.70	12.17 12.10

(Table 1 cont'd.....)

12	C ₂ H ₅	4,6-dimethyl-	333-5	67	483	C ₂₃ H ₂₅ N ₅ O ₅ S	57.14	5.18	14.49
							57.00	5.10	14.80
13	C ₃ H ₇ (n)	H	280	71	391	C ₁₈ H ₂₁ N ₃ O ₅ S	55.24	5.37	10.74
							55.00	5.30	10.70
14	C ₃ H ₇ (n)	-COCH ₃	266	67	433	C ₂₀ H ₂₃ N ₃ O ₆ S	55.42	5.31	9.70
							55.20	5.30	10.00
15	C ₃ H ₇ (n)	-C(=NH)NH ₂	251-3	61	433	C ₁₉ H ₂₃ N ₅ O ₅ S	52.66	5.31	16.17
							52.90	5.30	16.00
16	C ₃ H ₇ (n)	2-pyrimidinyl	310-2	65	469	C ₂₂ H ₂₃ N ₅ O ₅ S	56.29	4.90	14.93
							56.00	5.00	14.50
17	C ₃ H ₇ (n)	2-thiazolyl	306-7	70	474	C ₂₁ H ₂₂ N ₄ O ₅ S ₂	53.16	4.64	11.81
							53.00	4.60	11.80
18	C ₃ H ₇ (n)	4,6-dimethyl 2-pyrimidinyl	345-7	56	497	C ₂₄ H ₂₇ N ₅ O ₅ S	57.95	5.43	14.08
							58.10	5.40	14.00
19	Benzyl	H	258-60	61	439	C ₂₂ H ₂₁ N ₃ O ₅ S	60.14	4.78	9.57
							60.00	4.40	9.30
20	Benzyl	-CO-CH ₃	270-2	65	481	C ₂₄ H ₂₃ N ₃ O ₆ S	59.88	4.78	8.73
							60.00	5.00	9.00
21	Benzyl	-C(=NH)NH ₂	285-7	66	481	C ₂₃ H ₂₃ N ₅ O ₅ S	57.38	4.78	14.55
							57.70	4.60	14.50
22	Benzyl	2-pyrimidinyl	310-2	71	517	C ₂₆ H ₂₃ N ₅ O ₅ S	60.35	4.45	13.54
							60.30	4.10	13.30
23	Benzyl	2-thiazolyl	322-2	72	522	C ₂₅ H ₂₂ N ₄ O ₅ S ₂	57.47	4.21	10.73
							57.40	4.00	10.50
24	Benzyl	4,6-dimethyl 2-pyrimidinyl	297-9	79	545	C ₂₈ H ₂₇ N ₅ O ₅ S	61.65	4.95	12.84
							61.50	4.50	12.70
25	Benzoyl	H	241-3	81	453	C ₂₂ H ₁₉ N ₃ O ₆ S	58.28	4.19	9.27
							58.00	4.00	9.00
26	Benzoyl	-CO-CH ₃	230-2	89	495	C ₂₄ H ₂₁ N ₃ O ₇ S	58.18	4.19	8.48
							58.30	3.90	8.50
27	Benzoyl	-C(=NH)NH ₂	262-4	77	495	C ₂₃ H ₂₁ N ₅ O ₆ S	58.18	4.19	8.48
							58.30	3.90	8.50
28	Benzoyl	2-pyrimidinyl	309-300	66	531	C ₂₆ H ₂₁ N ₅ O ₆ S	58.75	3.75	10.45
							58.30	4.00	13.40
29	Benzoyl	2-thiazolyl	303-5	60	536	C ₂₅ H ₂₀ N ₄ O ₆ S ₂	55.97	3.73	10.45
							55.50	4.00	10.90
30	Benzoyl	4,6-dimethyl 2-pyrimidinyl	345-7	63	559	C ₂₈ H ₂₅ N ₅ O ₆ S	60.11	4.47	12.52
							59.90	4.30	12.50
31	Phenyl	H	222-4	75	425	C ₂₁ H ₁₉ N ₃ O ₅ S	59.29	4.47	9.88
							59.00	4.00	10.00
32	Phenyl	-CO-CH ₃	250-2	75	467	C ₂₃ H ₂₂ N ₃ O ₆ S	59.10	4.50	8.99
							59.00	4.70	9.00
33	Phenyl	-C(=NH)NH ₂	275-7	76	467	C ₂₂ H ₂₁ N ₅ O ₅ S	56.53	4.50	14.99
							56.30	4.90	15.00
34	Phenyl	2-pyrimidinyl	295-7	60	503	C ₂₅ H ₂₁ N ₅ O ₅ S	59.64	4.17	13.91
							60.00	4.00	13.70
35	Phenyl	2-thiazolyl	277-9	61	508	C ₂₄ H ₂₀ N ₄ O ₅ S ₂	56.69	3.94	11.02
							57.00	4.00	11.00
36	Phenyl	4-6-dimethyl 2-pyrimidinyl	330-3	65	531	C ₂₇ H ₂₅ N ₅ O ₅ S	61.10	4.71	13.18
							61.00	5.00	13.00

Table 2
Spectral data of some representatives (**III**)

Comp.	IR (Kbr)cm ⁻¹ , ¹ HNMR (δppm, DFMSO)
III ₁	¹ HNMR: 2.40 (s,3H, NH-CH ₃), 3.20 (s, 1H, NH-CH ₃), 5.00 (s, 2H,COOCH ₂ -), 7.20-8.20 (m, 8H, aromatic protons), 7.30 (s, 2H, SO ₂ -NH ₂). IR: 3385-3200 (NH) 1740-1714(COO ester) 1685-1660 (amidic NH), 1335, 1160 for (SO ₂).
III ₂	¹ HNMR: 2.40(s,3H, NH-CH ₃), 3.20 (s, 1H, NH- CH ₃), 5.2 (s, 2H, COO-CH ₂ -), 10.20 (s, 1H, NH-CO-CH ₃), 3.60 (s, 3H, NH-CO-CH ₃), 7.20-8.30 (m, 8H, aromatic protons). IR: 3385-3200 (NH) 1740-1714 (COO ester) 1685-1660 (amidic NH), 1335, 1160 for (SO ₂).
III ₇	¹ HNMR: 1.45 (t, 3H, CH ₂ -CH ₃), 2.60 (s, 1H, NH-CH ₃), 3.45 (q, 2H, NH ₂ -CH ₃), 5.2 (s, 2H, COO-CH ₂ -COO), 10.7 (s, 2H, SO ₂ , NH ₂), 7.20-8.30 (m, 8H, aromatic protons). IR: 3385-3200 (NH) 1740-1714 (COO ester) 1685-1660 (amidic NH), (1335, 1160) for (SO ₂).
III ₁₃	¹ HNMR: 1.25 (t, 3H-CH ₂ -CH ₃), 1.85 (m, 2H, CH ₂ -CH ₂ -CH ₃), 3.65 (q, 2H, NH-CH ₂ -CH ₂), 2.60 (s, 1H, NH, CH ₂), 5.00 (s, 2H,COO-CH ₂), 11.20 (s, 2H, SO ₂ NH ₂), 7.20-8.30 (m, 8H, aromatic protons). IR: 3385-3200 (NH) 1740-1714 (COO ester) 1685-1660 (amidic NH), (1335, 1160) for (SO ₂).
III ₁₉	¹ HNMR: 2.60 (s, 1H, NH-Ch ₂ -ph), 4.70 (s, 2H, NH-Ch ₂ -ph), 5.30 (s,2H, COOCH ₂), 10.70 (s, 1H, SO ₂ -NH ₂), 7.10-8.30 (m, 13H, aromatic protons). IR: 3385-3200 (NH) 1740-1714 (COO ester) 1685-1660 (amidic NH), 1335, 1160 for (SO ₂).
III ₂₅	¹ HNMR: 5.00 (s,2H, COOCH ₂), 10.90 (s, 2H, SO ₂ NH ₂), 11.90 (s, 1H, NH-Co-ph), 7.20-8.30 (m, 13H, aromatic protons) IR 3385-3200 (NH) 1740-1714 COO ester) 1685-1660 (amidic NH), (1335, 1160) for (SO ₂).
III ₂₆	IR: 3385-3200 (NH) 1740-1714 (COO ester) 1685-1660 (amidic NH), (1335, 1160) for (SO ₂).
III ₃₁	¹ HNMR: 5.20 (s, 2H, COOCH ₂ CO), 3.60 (s, 1H, NH-ph), 11.90 (s, 2H, SO ₂ NH ₂), 7.20-8.30 (m, 13H, aromatic protons) IR: 3385-3200 (NH) 1740-1714, (COO ester) 1685-1660 (amidic NH), (1335, 1160) for (SO ₂).
III ₃₆	IR: 3385-3200 (NH) 1740-1714 (COO ester) 1685-1660 (amidic NH), (1335, 1160) for (SO ₂).

corresponding N⁴-chloroacetylaminobenzenesulfonamide derivatives (**II**), as reported (Jacobs *et al* 1919; El-Moghazy 1992). The reaction of (**I**) and (**II**) occurred smoothly in dimethyl formamide giving the final new esters (**III**). The structures of the latter were substantiated from microanalytical and spectral data Table (1&2). Table 2 includes spectral data of some representatives compound (**III**). The IR spectra of (**III**) in KBr are characterized by strong absorption bands near 3385-33200 cm⁻¹ due to (NH); and 1740-1714 cm⁻¹ due to carbonyl ester and near 1335, 1160 cm⁻¹ due to SO₂ absorption. The ¹HNMR spectra of (**III**) in DMSO are characterized by the presence of a singlet of one proton at δ 9.50 ppm (due to CON⁴H) all spectra showed a singlet of two protons at δ 5.20 ppm due to (-O-CH₂-CO). The aromatic protons displayed their resonances in the expected region.

The preliminary pharmacological evaluation of Compound (**III**) showed that compounds (**III**)_{1,3,7,14,18,25,31,32,35,36} possess analgesic action similar to that of paracetamol. Compound (**III**)_{2,21,26,30} are less active while the remaining derivatives were found to be inactive, (Table 3). Compounds bearing sulfanilamide, sulfacetamide, sulfaguanidine and sulfadimidine moieties showed antipyretic action comparable to that of paracetamol, where they decreased the body temperature to 35.5°C. (Table 4). Compounds (**III**)_{1,2,9,13,21,27,30,31} possess antispasmodic effects higher than the action of the reference compound (atropine) while compound (**III**)_{8,19,32} possess similar antispasmodic effect of atropine the remaining compounds are less active (Table 5). When the contraction of the isolated rabbit intestine induced by the effect of acetylcholine, compounds (**III**)_{2,3,6,8,14,15} possess higher spasmolytic action than the atropine while compound

Table 3

Result of analgesic activity of compound (III)

Comp. (III)	% Protection against writhing after			
	30 min.	60 min.	120 min.	180 min.
Control	0.0	0.0	00	0.0
paracetamol	100	100	100	100
1	100	100	100	100
2	83.3	83.3	83.3	83.3
3	100	100	100	100
4	0.0	0.0	0.0	0.0
5	0.0	0.0	0.0	0.0
6	0.0	0.0	0.0	0.0
7	100	100	100	100
8	100	100	100	100
9	0.0	0.0	0.0	0.0
10	0.0	0.0	0.0	0.0
11	0.0	0.0	0.0	0.0
12	83.3	83.3	83.3	83.3
13	83.3	83.3	83.3	83.3
14	100	100	100	100
15	0.0	0.0	0.0	0.0
16	0.0	0.0	0.0	0.0
17	0.0	0.0	0.0	0.0
18	100	100	100	100
19	100	100	100	100
20	66.6	66.6	66.6	66.6
21	83.3	83.3	83.3	83.3
22	0.0	0.0	0.0	0.0
23	0.0	0.0	0.0	0.0
24	66.6	66.6	66.6	66.6
25	100	100	100	100
26	83.3	83.3	83.3	83.3
27	83.3	83.3	83.3	83.3
28	0.0	0.0	0.0	0.0
29	0.0	0.0	0.0	0.0
30	66.6	66.6	66.6	66.6
31	100	100	100	100
32	100	100	100	100
33	0.0	0.0	0.0	0.0
34	0.0	0.0	0.0	0.0
35	100	100	100	100
36	100	100	100	100

(III)_{1,15,19,20,27} equal to the action of atropine the remaining compounds are inactive (Table 6).

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Table 4

Result of analgesic activity of compound (III)

Comp. (III)	Rectal temp.	Comp. (III)	Rectal temp.
Control	38.88±0.65	18	34.66±0.06
paracetamol	35.05±0.25	19	35.68±0.32
1	35.8±0.3	20	35.66±0.12
2	35.36±0.36	21	35.12±0.04
3	35.47±0.17	22	38.88±0.65
4	38.88±0.65	23	38.88±0.65
5	38.88±0.65	24	38.88±0.35
6	35.66±0.12	25	35.36±0.36
7	34.86±0.06	26	35.05±0.25
8	35.55±0.4	27	38.88±0.65
9	35.32±0.12	28	38.88±0.65
10	38.88±0.65	29	38.88±0.65
11	38.88±0.65	30	35.75±0.35
12	35.68±0.32	31	35.8±0.3
13	35.05±0.25	32	35.55±0.4
14	35.03±0.3	33	38.88±0.65
15	38.88±0.65	34	38.88±0.65
16	38.88±0.65	35	38.88±0.65
17	38.88±0.65	36	35.8±0.2

Table 5

Effect of atropine (standard) and compound (III) at a dose of 5 mg bath⁻¹ on a normal contraction of isolated rabbit intestine

Comp. (III)	Response(MM) X±S.E	Comp. (III)	Response X±S.E
Atropine	4±0.1	19	4±0.1
1	8±0.15	20	3±0.1
2	7±0.6	21	6±0.3
3	2.5±0.25	22	2.5±0.25
4	2.5±0.25	23	2.5±0.25
5	2.5±0.25	24	2.5±0.25
6	2.5±0.25	25	3.5±0.25
7	3.5±0.25	26	2.5±0.25
8	4±0.6	27	8±0.6
9	6±0.6	28	2.5±0.25
10	2.5±0.25	29	2.5±0.25
11	2.5±0.25	30	7±0.6
12	2.5±0.25	31	5±0.2
13	5±0.5	32	4±0.6
14	3±0.2	33	2.5±0.25
15	6±0.6	34	2.5±0.25
16	2.5±0.25	35	2.5±0.25
17	2.5±0.25	36	3±0.1
18	2.5±0.25		

P>0.05 The height of normal contraction was (10 mm±0.1).

Table 6

Effect of atropine (standard) and tested compounds (III) at a dose of 5 mg bath⁻¹ on acetylcholine induced contraction of isolated Rabbit intestine

Comp. (III)	Response(MM) X±S.E	Comp. (III)	Response X±S.E
Atropine	13±0.8	19	14±0.9
1	13±1.2	20	13±0.8
2	16±1.2	21	13±0.8
3	16±0.9	22	11±1.1
4	3±0.2	23	3±0.2
5	3±0.2	24	3±0.2
6	15±0.8	25	3±0.2
7	14±0.5	26	11±1.1
8	16±0.8	27	13±0.9
9	12±1.1	28	12±1.2
10	3±0.2	29	3±0.2
11	3±0.2	30	10±1.3
12	3±0.2	31	10±1.3
13	9±1.1	32	10±1.2
14	15±0.6	33	3±0.2
15	16±0.8	34	3±0.2
16	3±0.2	35	3±0.2
17	3±0.2	36	12±1.2
18	9±1.1		

P>0.05 The hight of contraction induced by acetylcholine was (25mm±0.5).

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