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Original research paper

Preparation of 4-aminophenylacetic acid derivatives with promising antimicrobial activity

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Condensation of 4-aminophenylacetic acid with phthalic anhydride gave (dioxoisoindolin-2-yl)phenylacetic acid (**1**), which was employed as the key intermediate in the synthesis of title compounds **2**–**8**. The products were characterized by analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra). Antimicrobial activities were studied and some of the compounds showed promising results.

Keywords: 4-aminophenylacetic acid, (dioxoisoindolin-2-yl)phenylacetic acid derivatives, {[(1*H*-benzo[d]imidazol-2-yl)/(4*H*-benzo[d][1,3]oxazin-2-yl)methyl]phenyl}isoindoline-1,3-diones, phthaloylhydrazide salts, antimicrobial activity

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Chlorambucil [*N*,*N*-bis(chloroethyl)-*p*-aminophenylbutyric acid] is widely clinically used as an anticancer drug and also as an immunosuppressant, and its biologically active β-oxidation product phenylacetic acid mustard [*N*,*N*-bis(2-chloroethyl)-4-aminophenylacetic acid] is a bifunctional aromatic alkylator (1–2).

Some pseudo-peptide analogs of *trans*-4-aminomethylcyclohexanecarbonyl-L-phenylalanyl-4-aminophenylacetic acid, a plasma kallikrein selective inhibitor, were synthesized and did not exhibit any detectable inhibitory activity against plasma kallikrein, plasmin, urikinase, thrombin or trypsin (3). 4-Aminophenylacetic acid (4-APAA), a peptidemimic lacking a peptide bond, has been shown to interact with a proton-coupled oligopeptide transporter in addition to inhibiting transport of labeled peptides (4). In view of the considerable importance of 4-APAA for formation of some medical compounds, we undertook synthesis of some newly heterocyclic compounds bearing 4-APAA moiety. Such compounds could possess interesting and useful biological properties.

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EXPERIMENTAL

Melting points were determined using the melting point apparatus (Stuart Scientific Co., UK) and remained uncorrected. The IR spectra were recorded on a Shimadzu IR 440 spectrophotometer (Shimadzu, Japan) in KBr. ^{1}H and ^{13}C NMR spectra were recoded on a Varian Gemini 200 NMR spectrometer (Varian, UK), at 200 and 50 MHz, with chemical shifts calculated from deuterated solvent residues. Microanalytical data were obtained from the Microanalytical Unit of the Cairo University (Egypt). Physicochemical data are given in Table I and spectral data in Table II.

Syntheses

*2-[4-(1,3-Dioxoisoindolin-2-yl)]phenylacetic acid (**1**)*

A mixture of 4-APAA (1 g, 0.00662 mol) and phthalic anhydride (0.980 g, 0.00662 mol) was refluxed in glacial acetic acid (10 mL) for 10 h. The solid obtained was filtered and washed with diluted ethanol.

*2-[4-(1,3-Dioxoisoindolin-2-yl)]phenylacetylchloride (**2**)*

A mixture of compound **1** (0.281 g, 0.001 mol) and an excess of thionyl chloride (10 mL) was refluxed for 1 h, then the excess thionyl chloride was evaporated under vacuo. The solid obtained was collected and washed several times with dry benzene and was used without further purification.

*Methyl-2-[4-(1,3-dioxoisoindolin-2-yl)]phenylacetate (**3**)*

A solution of **2** (0.3 g, 0.001 mol) in dry methanol (20 mL) containing dry pyridine (1 mL) was refluxed. The solid obtained was collected by filtration.

*2-{4-[(1H-benzo[d]imidazol-2-yl)methyl]phenyl}isoindoline-1,3-diones (**4a**,**b**),*
*N-(2-hydroxyphenyl)-2-[4-(1,3-dioxoisoindolin-2-yl)phenyl]acetamide (**5a**),*
*2-{2-[4-(1,3-dioxoisoindolin-2-yl)phenyl]acetamido}benzoic acid (**5b**),*
*2-{2-[4-(1,3-dioxoisoindolin-2-yl)phenyl]acetamido}benzoate (**5c**),*
*bis-{[4-(1,3-dioxoisoindolin-2-yl)phenyl]acetyl}-p-phenylenediamine (**6**),*
*N,N'-bis-{2-[4-(1,3-dioxoisoindolin-2-yl)phenyl]acetamido}biphenyl (**7**),*
*N-(4-sulfanoyl)-2-[4-(1,3-dioxoisoindolin-2-yl)phenyl]acetamide (**8**)*

General procedure. – Solution of acid chloride **2** [0.3 g, 0.001 mol, in case of compounds **4, 5, 8** and 0.6 g (0.002 mol) in case of compunds **6, 7**] in dry benzene (20 mL) and aromatic amine derivatives (0.001 mol) were refluxed for 30 min. The solid obtained was filtered and washed with cold water several times and then recrystallized from a suitable solvent.

Table I. Physicochemical data of the newly synthesized compounds

Compd. No.	M. p. (solvent)	Color (yield, %)	Molecular formula (M_r)	Elemental analysis (%) Calcd./found		
				C	H	N
1	218–220 (GAA)[a]	Colorless (89)	$C_{16}H_{11}NO_4$ (281.26)	68.32 68.25	3.94 3.88	4.98 4.91
2	178–180	Colorless (96)	$C_{16}H_{10}ClNO_3$ 299.71	64.12 64.08	3.36 3.27	4.67 4.69
3	138–140 (ethanol)	Colorless (81)	$C_{17}H_{13}NO_4$ 295.29	69.15 69.06	4.44 4.36	4.74 4.65
4a	240–242 (GAA)	Colorless (88)	$C_{22}H_{15}N_3O_2$ (353.37)	74.78 74.69	4.28 4.22	11.89 11.82
4b	270–272 (GAA)	Colorless (86)	$C_{24}H_{19}N_3O_2$ (381.43)	75.57 75.51	5.02 4.95	11.02 1098
5a	210–212 (benzene)	Yellow (60)	$C_{22}H_{16}N_2O_4$ (372.37)	70.96 70.89	4.33 4.27	7.52 7.45
5b	238–240 (benzene)	Colorless (95)	$C_{23}H_{16}N_2O_5$ (400.38)	69.00 68.95	4.03 3.99	7.00 6.91
5c	220–222 (GAA)	Colorless (65)	$C_{24}H_{18}N_2O_5$ (414.41)	69.56 69.51	4.38 4.32	6.76 6.69
6	> 300 (GAA)	Colorless (81)	$C_{38}H_{26}N_4O_6$ (634.64)	71.92 71.88	4.13 4.6	8.83 8.79
7	230–232 (GAA)	Yellow (90)	$C_{44}H_{30}N_4O_6$ (710.73)	74.36 74.31	4.25 4.20	7.88 7.81
8	270–272 (GAA)	Yellow (65)	$C_{22}H_{17}N_3O_5S$ (435.45)	60.68 60.61	3.93 3.86	9.65 9.60
9	210–212 (GAA)	Colorless (89)	$C_{23}H_{14}N_2O_4$ 382.37	72.25 72.05	3.69 3.51	7.33 7.24
10	226–228 (ethanol)	Colorless (68)	$C_{23}H_{20}N_4O_5$ (432.43)	63.88 63.80	4.66 4.61	12.96 12.89
11	308–310 (ethanol)	Colorless (60)	$C_{30}H_{28}N_6O_4$ (536.58)	67.15 67.8	5.26 5.19	15.66 15.59
12	252–254 (ethanol)	Colorless (65)	$C_{28}H_{25}N_5O_3$ (479.53)	70.13 70.6	5.25 5.18	14.60 14.54
13	220–222 (ethanol)	Colorless (70)	$C_{14}H_{15}N_3O_3S$ (305.35)	55.07 55.00	4.95 4.89	13.76 13.70
14	178–180 (ethanol)	Colorless (80)	$C_{18}H_{18}N_2O_4$ 326.35	66.25 66.18	5.56 5.51	8.58 8.52

[a] Glacial acetic acid

Table II. Spectral data of prepared compounds

Compd. No.	IR (ν, cm^{-1})	^1H NMR/^{13}C NMR (δ, ppm) (DMSO-d6) / MS
1	3432 (br, OH), 2925 (CH aliph.), 1785, 1716 (CO)	3.773 (s, 2H, CH_2), 7.411 (s, 4H, Ar-H-*p*-subst.), 7.953 (m, 4H, Ar-H), 10.793 (s, br, 1H, COOH)
3	2956 (stretching CH), 1736, 1710 (CO)	3.762 (s, 2H, CH_2), 3.639 (s, 3H, OCH_3), 7.399 (s, 4H, Ar-H-*p*-subst.), 7.93 (m, 4H, Ar-H) 38.674 (CH_2), 51.745 (CH_3O), 123.376, 127.26 (2C-3', 2C-2') 129.839, 134.664 (2C-5,6, 2C-4,7), 130.56 (C-4'), 131.524 (C-1'), 134.315 (C-3a', C-7a'), 166.99 (2CO), 171.421 (CO) *m/z* 295 (97), 236.9 (100), 130 (56), 104 (16), 76 (28)
4a	3239 (NH), 2925 (stretching CH), 1711, 1653 (CO)	3.748 (s, 2H, CH_2), two sets of multiplets at (7.162, 7.5) & 7.79 (12H, Ar-H), 9.6 (s, 1H, NH) *m/z* 353 (100), 325 (10), 263 (32), 236 (24), 206 (23), 179 (36), 135 (24), 104 (36), 76 (44)
4b	3332 (NH), 2925 (stretching CH), 1717 (CO)	2.156 (s, 6H, $2CH_3$), 3.723 (s, 2H, CH_2), two sets of multiplets at (7.274–7.526), (7.891–7.897) (10 H, Ar-H), 9.602 (s, 1H, NH) 19.806 ($2CH_3$), 39.61 (CH_2), 113.544 (C-4'', 7''), 123.376 (C-3', 5'), 127.237 (C-4, 7), 129.619 (C-2', 6'), 135.954 (C-5, 6), 131.508 (C-1', 4', 3a', 7a'), 135.954 (C-3a'', 1a'', C-2''), 169.001 (2CO)
5a	3378 (NH), 4025 (br) (OH), 2925 (stretching CH), 1721, 1654 (CO)	3.826 (s, 2H, CH_2), three sets of multiplets at (6.711–6.973), (7.371–7.512), (7.889–7.973) (12H, Ar-H), 9.452 (s, 1H, OH), 9.798 (s, 1H, NH) 42.383 (CH_2), 115.531 (C-3''), 118.9 (C-5''), 122.147 (C-6''), 123.368 (C-3', 5'), 124.582 (C-4''), 127.214 (C-4, 7), 129.627 (C-2', 6'), 136.159 (C-5, 6), 126.228 (C-1''), 130.279 (C-1'), 131.524 (C-4'), 147.766 (C-2''), 167.013 (CO-1, 3), 169.243 (CONH) *m/z* 354 $M^+ - H_2O$, 236 (53.69), 224 (30.85), 195 (24.24), 130 (39.86), 109 (95.58), 106 (81.5), 104 (27.64), 90 (8.74), 80 (40.61), 76 (83.82), 43 (75.89)
5b	3446 (OH), 3285 (NH), 2924 (stretching CH), at 1711, 1691 and 1664 (CO)	3.836 (s, 2H, CH_2), 7.117, 7.12 (dd, J_1 = 7.4, J_2 = 1.2 Hz, 1H, Ar-H), 7.155, 7.158 (dd, J_1 = 7.8, J_2 = 1.2 Hz, 1H, Ar-H), 7.459 (AB-q, *J* = 8.4 Hz, 4H, Ar-H), 7.592 (m, 1H, Ar-H), 8.45 (d, *J* = 8.6 Hz, 2H, Ar-H), 11.241 (s, 1H, N-H), 13.616 (s, br, 1H, COOH). 43.961 (CH_2), 116.768 (C-COOH), 120.083 (C-6''), 122.784 (C-3', 5'), 123.368(C-4''), 127.283 (C-4, 7), 129.862 (C-2', 6'), 131.008 (C-3''), 133.944 (C-5''), 134.649 (C-5, 6), 130.575 (C-1'), 131.501 (C-4'), 135.006 (C-3a, 7a), 140.605 (C1''), 166.96 (CO-1, 3), 169.114 (COOH), 169.395 (CONH)
5c	3256 (NH), 3038 (C-H arom.), at 2956 (C-H aliphatic), 1730, 1682 (CO), with two shoulders at 1786, 1770	3.8 (s, 3H, OCH_3), 3.818 (s, 2H, CH_2), 7.169, 7.172 (dd, J_1 = 6.6, J_2 = 1.2 Hz, 1H, Ar-H), 7.207, 7.21 (dd, J_1 = 7.4, J_2 = 1.2 Hz), 7.459 (AB-q, *J* = 8.6Hz, 4 H, Ar-H), 7.594 (m, 1H, Ar-H), (7.856–7.989) (m, 3H, Ar-H), 8.204 (d, J = 8.6, 2H, Ar-H) and 10.663 (s, 1H, NH)

Table II. contd.

Compd. No.	IR (ν, cm^{-1})	^1H NMR/^{13}C NMR (δ, ppm) (DMSO-d6) / MS
6	3313 (NH), 2924, 2854 (CH aliph.), 1719, 1663 (CO)	3.685 (s, 4H, $2CH_2$), 7.418 (AB-q, *J* = 8.6 Hz, 4H, Ar-H), 7.524 (s, 8H, Ar-H), 7.927 (m, 8H, Ar-H), 10.163 (s, 2H, NH; cancelled by D_2O) [M^+-$C_6H_4(CO)_2$] at *m/z* 502 (4%), 371 (28), 263 (44), 236 (100), 180 (24), 132 (18), 108 (48), 83 (14.6), 76 (24)
7	3316 (NH), 2924 (CH aliph.), 1720, 1663 (CO)	3.744 (s, 4H, $2CH_2$), 7.439 (AB-q, *J* = 8.6 Hz, 8H, Ar-H), 7.639 (AB-q, *J* = 9Hz, 8H, Ar-H), (7.901–7.985) (m, 8H, Ar-H), 10.317 (s, 2H, 2NH) 43.961 ($2CH_2$), (119.484, 123.368, 127.252, 129.597, 134.657, 130.317, 131.531, 134.452, 135.946, 138.23) (C-Ar), 167.013 (CO), 168.819 (CONH)
8	3330, 3232 (NH), 2922 (CH aliph.), 1738, 1720, 1684 (CO), 1316, 1156 (SO_2)	3.767 (s, 2H, CH_2), 7.248 (s, 2H, SO_2NH_2), 7.434 (AB-q, *J* = 8.6 Hz, 4H, Ar-H), 7.758 (s, 4H, Ar-H), 7.928 (m, 4H, Ar-H), 10.559 (s, 1H, NH) *m/z* 435 (M^+, 30.45), 236 (100), 263 (45.31), 193 (5.22), 171 (4.67), 130 (15.33), 76 (3.32)
9	2926 (C-H aliph.), 1762, 1718 (CO)	4.127 (s, 2H, CH_2), two sets of multiples at (7.354–7.645), (7.879–7.995) (m, 12H, Ar-H)
10	3275, 3250, 3153 (NH, COOH), 1664 (CO)	3.836 (s, 2H, CH_2), 6.527, 6.984 (AB-q, *J* = 8.2 Hz, 4H, Ar-H), 7.052, 7.055, 7.128 (ddd, *J* = 1.2, 8.6, 7.8 Hz, 1H, Ar-H), 7.409 (d, *J* = 8.6 Hz, 1H, Ar-H), (7.447–7.586) (m, 1H, Ar-H), 7.852, 7.881 (dd, J_1 = 3.2, J_2 = 5.8 Hz, 2H, Ar-H), 8.05 & 8.053 (dd, J_1 = 3.6, J_2 = 5.8 Hz, 2H, Ar-H), 7.927 (d, *J* = 7.8 Hz,1H, Ar-H), 11.126 (s, 1H, COOH) *m/z* 432 (M^+, 0), 270 (12), 133 (14), 106 (100), 77 (8) [for phthalohydrazide at *m/z 162 (8)*]
11	3280, 3152 (NH), 2940 (CH aliph.), 1659 (CO)	3.365 (s, 4H, $2CH_2$), 3.946 (broad band, 4H, NH, $^+NH_3$, NH_2), 6.484, 6.949 (ABq, *J* = 8.2 Hz, 8H, Ar-H), 7.475 (s, 4H,Ar-H), 7.797, 7.803 (dd, J_1 = 3.4, J_2 = 5.8 Hz, 2H,6 & 7-Ar-H), 8.045, 8.051 (dd, J_1 = 3.4, J_2 = 5.8 Hz, 2H, 5 & 8-Ar-H), 9.952 (s, 2H, 2NH) *m/z* 536 (M^+, 0), 374 (20), 241 (22), 133 (6), 108 (24), 106 (100), 77 (12) [beside a molecular ion peak for phthaloylhydrazide at *m/z* 162 (12)]
12	(2550–3150), (NH_2, NH_3, NH) 1662 (CO)	3.418 (s, 2H, CH_2), 6.502, 6.978 (q, *J* = 8.4 Hz, 4H, Ar-H), (6.582–6.657), (7.457–7.68) (m, H, NH_3, NH_2), 7.853, 7.870 (dd, J_1 = 3.2, J_2 = 6 Hz, 2H, 6-, 7- Ar-H), 8.05, 8.081 (dd, J_1 = 3.2, J_2 = 6 Hz, 2H, 5-, 8-ArH) *m/z* 479 (M^+, 0), 317 (50), 184 (38), 133 (9), 106 (100), 77 (25) [together with the molecular ion peak of phthalhydrazide at *m/z* 162 (16)]

Table II. contd.

Compd. No.	IR (ν, cm^{-1})	^1H NMR/^{13}C NMR (δ, ppm) (DMSO-d6) / MS
13	3100, 3332, 3290, 3260, 3190, 3120 (NH, NH_2), 1664 (CO), 1336, 1158 (SO_2)	3.435 (s, 2H, CH_2), 4.93 (s, br, 2H, NH_2), 6.488, 6.955 (AB-q, *J* = 8.2 Hz, 4H, Ar-H), 7.223 (s, br, 2H, SO_2NH_2), 7.726 (s, 4H, Ar-H), 10.327 (s, 1H, NH) *m/z* 305 (7.46), 199 (3.28), 133 (2.4), 108 (2.4), 106 (100), 91 (11.38), 77 (12.74), 64 (14.25)
14	3328, 3126 (NH), 2922 (CH aliph.), 1714, 1676, 1662 (CO)	2.017 (s, 3H, NHCO**CH_3**), 3.656 (s, 2H, CH_2), 3.752 (s, 3H, OCH_3), 4 sets of multiples at (7.114–7.272), (7.434–7.561), (7.84–8.04), (8.057–8.254), (8H, Ar-H), 9.913 (s, 1H, NH), 10.585 (s, 1H, NH) *m/z* 326 (11.82), 175 (84.95), 151 (15.73), 149 (72.54), 146 (83.591), 133 (21.38), 119 (20.79), 106 (100), 90 (16.75), 77 (12.24)

*2-{4-[(4-Oxo-4*H*-benzo[d][1,3]oxazin-2-yl)methyl]phenyl}isoindoline-1,3-dione (**9**)*

To a solution of **5b** (1 g, 0.0025 mol) in dry benzene (15 mL), acetic anhydride (5 mL) was added. The reaction mixture was refluxed for 3 hours, then cooled. The solid so obtained was filtered off and washed with cold ethanol to give **9**.

*2-[2-(4-Aminophenyl)acetamido]benzoic acid with phthaloylhydrazide salt (**10**), (bis-4-Aminophenylaceto)-4-phenylenediamine mono phthaloylhydrazide salt (**11**), 4-Aminodiphenylaminocarbonylmethylanilinium phthaloylhydrazide salt (**12**), N-(4-sulfomoyl)-4-aminophenylacetamide (**13**)*

General procedure. – Hydrazine hydrate 25% (1.5 mL, 0.0075 mol) was added to the *N*-substituted phthalimide (**5b, 6–8)** (0.0075 mol) in ethanol and the mixture was refluxed for 40 min. After cooling, the product was collected by filtration.

*Methyl-2-(4-acetylaminophenyl)acetamidobenzoate (**14**)*

To a solution of **5c** (0.414 g, 0.001 mol) in glacial acetic acid (20 mL), hydrazine hydrate 99% (1 mL, 0.002 mol) was added. The reaction mixture was refluxed for 1 h and then evaporated under vacuo. The solid obtained was washed with diluted ethanol several times and collected by filtration.

Antimicrobial activity

Newly synthesized compounds were screened for their antimicrobial activity using *Bacillus subtilis* (ATCC-7972) (BS), *Staphylococcus aureus* (NCTC-7447) (SA) (Gram-positive), *Escherichia coli* (NCTC-10416) (EC), *Pseudomonas aeruginosa* (ATCC-10415) (PA) (Gram--negative) and *Candida albicans* (IMRU-3669) (CA), *Aspergillus niger* (ATCC-6275) (AN) (fungi) microorganisms. The activities of these compounds were tested using the disc diffusion method (5, 6). The tested compounds were dissolved in *N*,*N*-dimethylformamide

Table III. Antimicrobial activity of new compounds

Compound No.[a]	Inhibition zone					
	Gram-positive		Gram-negative		Fungi	
	BS	SA	EC	PA	CA	AN
3	+++	+++	++	++	+	–
4a	++	++	++	++	–	–
4b	+++	+++	+++	+++	++	+
5a	–	–	–	–	–	–
5b	+	+	+	+	–	–
5c	+++	+++	+++	+++	++	++
7	++	++	++	++	–	–
8	+++	+++	+++	+++	++	++
14	+++	+++	+++	+++	++	+
Neomycin[b]	++++	++++	+++	+++	–	–

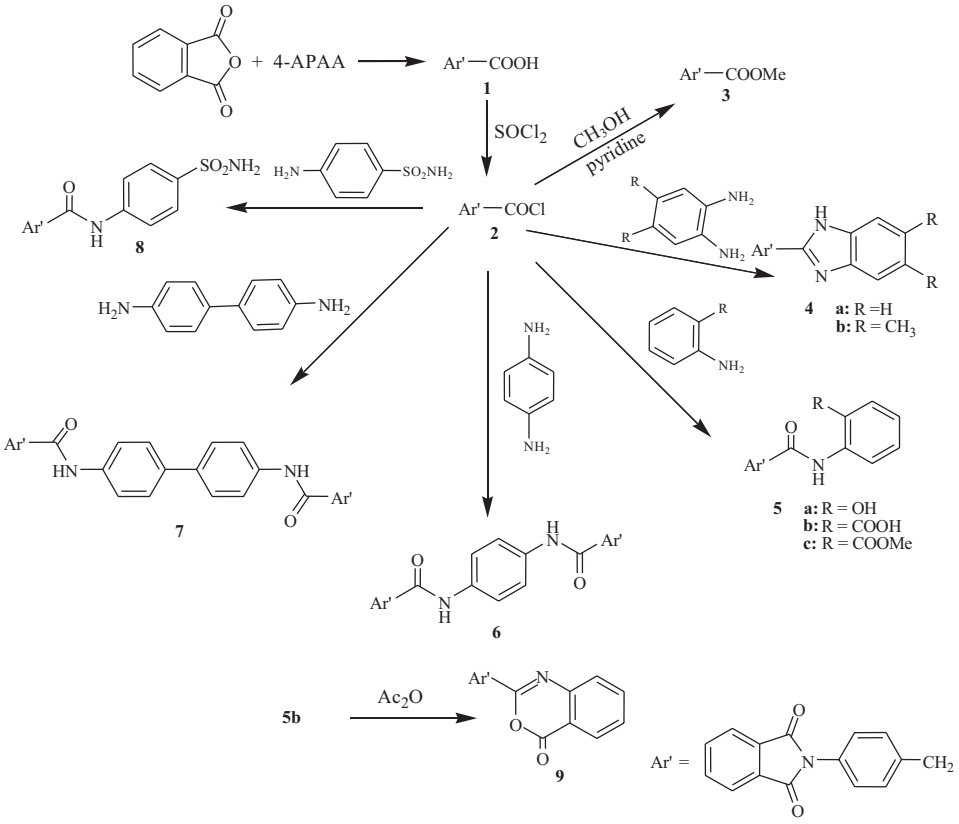
– no activity, + inhibition zone up to 8 mm), ++ inhibition zone 8–12 mm), +++ inhibition zone 12–15 mm), ++++ inhibition over 15 mm), [a] 1 mg mL^{-1} in DMF, [b] 30 μg mL^{-1} in DMF, DMF shows no activity.

(DMF) to get a solution of 1 mg mL^{-1}. Inhibition zones were measured in millimeters at the end of an incubation period of 48 h at 28 °C. DMF showed no inhibition zone. Neomycin in DMF (30 μg mL^{-1}) was used as a reference antibiotic.

RESULTS AND DISCUSSION

Condensation of 4-APAA with phthalic anhydride gave the corresponding 2-[4-(1,3--dioxoisoindolin-2-yl)phenyl]acetic acid (**1**), which on treatment with thionyl chloride afforded the corresponding acid chloride **2**. Treatment of **2** with methanol in pyridine afforded the corresponding methyl ester **3**, its ^{1}H NMR (δ ppm) showed a singlet signal at 3.64 corresponding to OCH_3 protons instead of carboxyl proton at 10.79 for compound 1. Also, condensation of **2** with *o*-phenylenediamines gave the corresponding benzo[d]-imidazolyl derivatives (**4a**,**b)** where NH proton resonated at 9.6 ppm. Also, treatment of **2** with *o*-aminophenol, anthranilic acid and their methyl ester gave the corresponding carboxamide derivatives **5a-c**, respectively. ^{1}H NMR for **5a** showed OH proton at 9.45 and NH at 9.80 ppm, for compound **5c** the methyl ester protons in the form of singlet signals at 3.8 beside NH at 10.66 ppm. When **5b** was boiled with acetic anhydride the corresponding benzoxazine derivative **9** resulted ^{1}H NMR revealed disappearance of δ OH and NH protons, which appeared for compound **5b** at 13.62 and 11.24 ppm, respectively.

Treatment of acid chloride **2** with *p*-phenylenediamine and/or benzidine gave the corresponding *N*,*N*′-biscarboxamide derivatives **6** and **7**, respectively. The mass spectra for compound **6** showed a molecular ion peak at *m*/*z* 502 (4) corresponding to $M^+ - C_6H_4(CO)_2$, indicating that one mol of *p*-phenylenediamine reacted with two moles of acid chloride **2**.

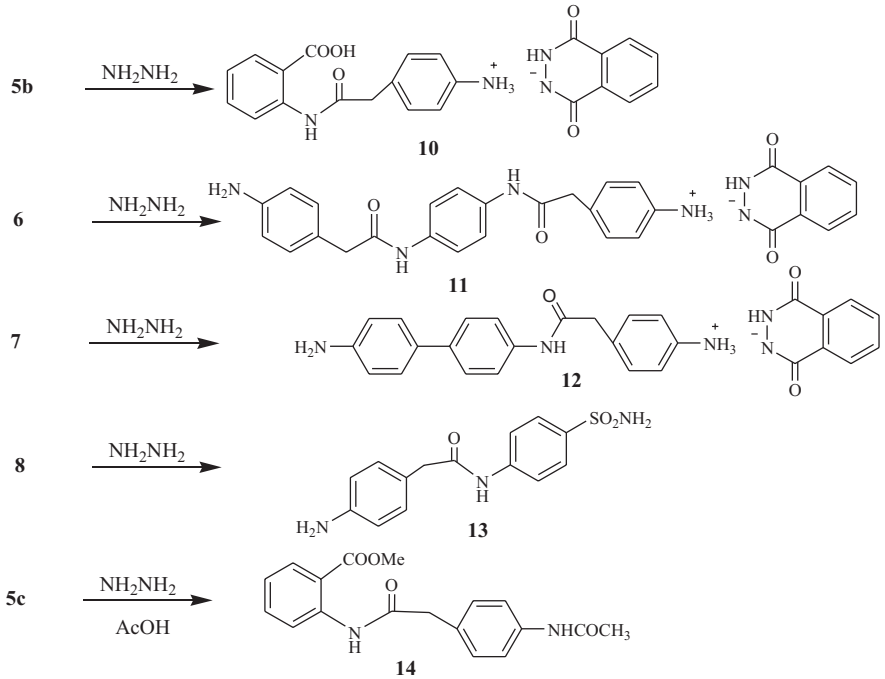


Scheme 1

When acid chloride **2** was treated with sulfanilamide, it gave the corresponding *p*-substituted carboxamide sulfanilamide (**8**) (Scheme 1). Its mass spectrum gave a molecular ion peak at *m/z* 435 (M^+, 30.45), while ^1H NMR showed δ NH at 10.56 and SO_2NH at 7.25 ppm.

Dephthaloylation (**7**) of 1,3-dioxoisoindolin-2-yl derivatives **5b**,**c**, **6**, **7** and **8** took place during the hydrazinolysis reaction. When compounds **5b**, **6** and **7** were treated with hydrazine hydrate, the corresponding mono ammonium salts with phthaloylhydrazide (**10**, **11** and **12)** were obtained, while treatment of **8** with hydrazine hydrate gave the corresponding N^4-(4-aminophenylacetyl)sulfanilamide (**13**). Also, treatment of **5c** with hydrazine hydrate, in acetic acid afforded the corresponding *N*-acetyl derivative **14** (Scheme 2).

Structures **1–14** were confirmed by spectral data (Table II) and the mass spectrum studies of these compounds gave additional evidence for the proposed structures (Schemes 3–5). The mass spectra of 1,3-dioxoisoindolin-2-yl phenylacetic acid derivatives **3**, **5**, **8** (Scheme 3) exhibit the common characteristic fragment peak at *m/z* 236 corresponding to methylphenylisoindoline-1,3-dione radical together with other lost fragments. The fragmentation pattern of anilinium salts gave a distinct molecular ion peak of phthaloylhydrazide at *m/z* 162.



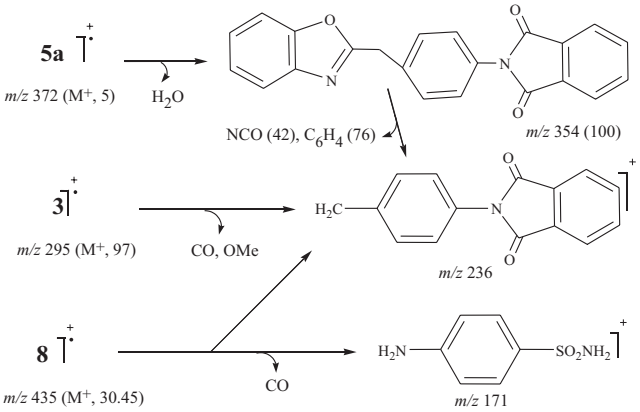
Scheme 2

Antimicrobial studies (Table III) showed that compounds **4b**, **5c**, **8** and **14** possess the highest antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, while compound **3** showed highest activity against BS and SA. Compounds **4b**, **5c**, **8** and **14** showed moderate activity against the fungus *Candida albicans* and compounds **5c** and **8** displayed moderate activity against the fungus *Aspergillus niger*. Compounds **3**, **4a**, **5a**, **5b**, **7** were weakly active against the tested microorganisms.

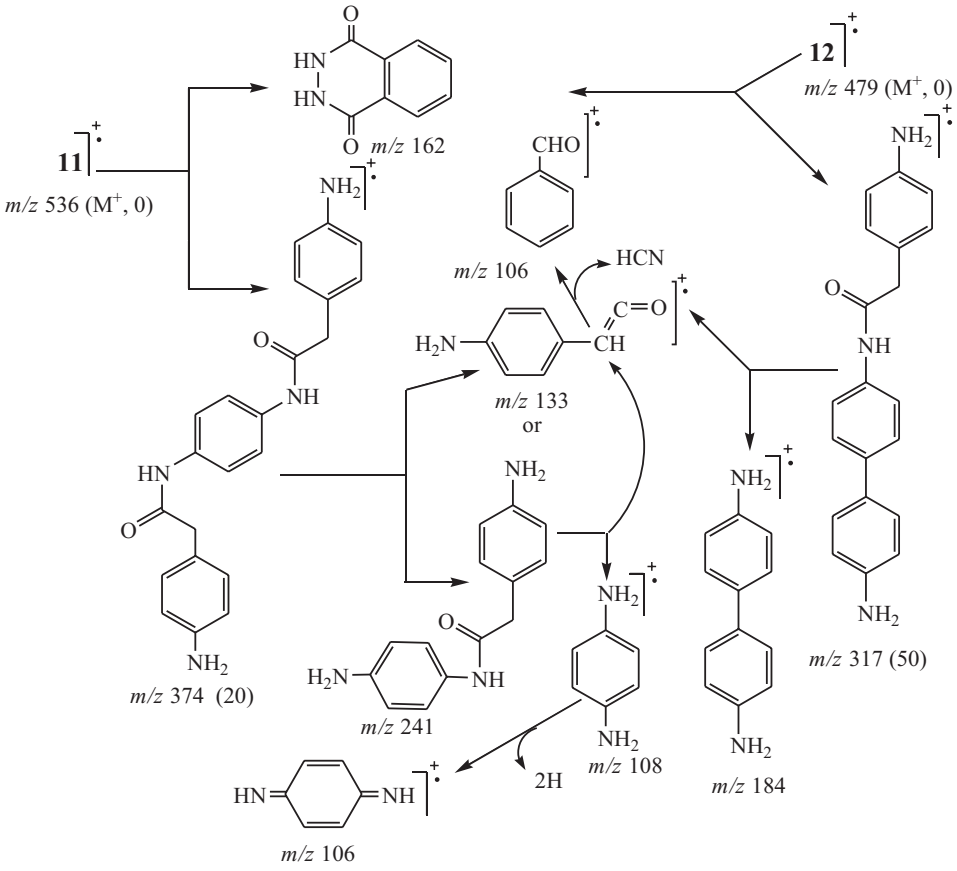
The present study revealed that substitution in *N*-phenylcarboxamide part at 2'-position with methoxycarbonyl (**5c**), at 4'-position with aminosulfonyl (**8**) caused a pronounced inhibition effect against Gram-positive (BS, SA) and Gram-negative (EC, BA) bacteria. The same effects were observed after transformation of CH_2CO_2H group into CH_2CO_2Me (**3**) and dimethylbenzoimidazol moiety (**4b**). The acetyl derivative of the new base **14**, obtained from **5c** by dephthaloylation, has a similar inhibition effect as compounds **4b**, **5** and **8**.

CONCLUSIONS

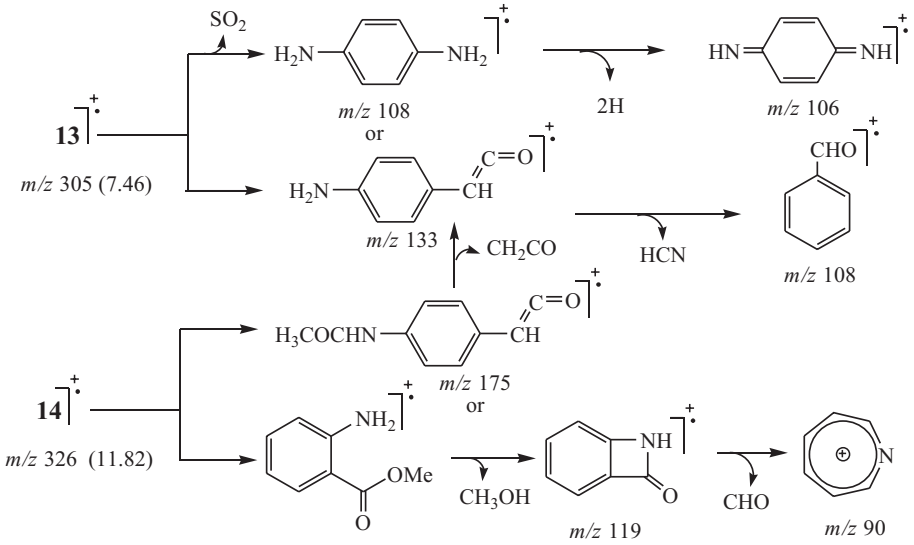
Evaluation of the new compounds established that the derivatives bearing 5,6-dimethylbenzoimidazolyl (**4b**), 2-methoxycarbonylphenylaminocarbonyl (**5c**, **14**) and 4-aminosulfonylphenylaminocarbonyl (**8**) moieties showed improved antifungal activity compared to neomycin and possessed antibacterial activity almost equivalent to the antibiotic used.



Scheme 3



Scheme 4



Scheme 5

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S A Ž E T A K

Priprava derivata 4-aminofeniloctene kiseline s antimikrobnim djelovanjem

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Kondenzacijom 4-APAA s anhidridom ftalne kiseline dobivena je (dioksoizoindolin-2-il)feniloctena kiselina 1, koja je upotrebljena kao ključni intermedijar u sintezi spojeva **2**–**8**. Produkti su karakterizirani analitičkim i spektroskopskim metodama (IR, ^{1}H NMR, ^{13}C NMR i MS). Neki od sintetiziranih spojeva imaju značajno antimikrobno djelovanje.

Ključne riječi: 4-aminofeniloctena kiselina, derivati (dioksoizoindolin-2-il)feniloctene kiseline, {[(1*H*-benzo[d]imidazol-2-il)/(4*H*-benzo[d][1,3]oksazin-2-il)metil]fenil}izoindolin-1,3-dioni, soli ftaloilhidrazida, antimikrobno djelovanje

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