SYNTHESIS OF 3,4-SUBSTITUTED PHENYLMETHYLENE-(2-CARBOXYPHENYL)AMINES AND THEIR ANTITUMOR ACTIVITY

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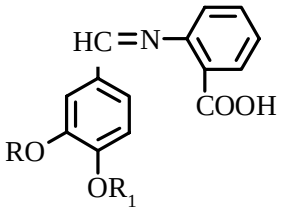
*Previously unknown azomethines **3a-z** and **4a-j** were prepared in methanol by condensation of anthranilic acid **1** with vanillin, vanillal, and esters of these compounds **2**.*

Key words: anthranilic acid, vanillin, vanillal, esters, azomethines.

Anthranilic (2-aminobenzoic) acid (**1**) is a pheromone for certain insects [1, 2] and also participates in metabolic processes [3-5]. Derivatives of anthranilic acid possess antimicrobial, anti-inflammatory, and antitumor activities and act as analgesics and local anesthetics [6-11].

Our goal was to prepare new and previously undescribed azomethines (Schiff bases) based on **1** and available natural aldehydophenols (vanillin, vanillal, and their esters **2**). Azomethines exhibit a broad spectrum of biological activity. They provide a basis for effective antidepressants, anticonvulsants, antimicrobials, soporifics, psychotropics, nematocidals, antitumorals, and other medicinal preparations [12]. 4-Hydroxy(alkyloyloxy, aryloyloxy)-3-methoxy(ethoxy)phenylmethylen-(2-carboxyphenyl)amines **3a-z** and **4a-j** were prepared by condensation of **1** with vanillin, vanillal, and their esters **2** in absolute methanol at the boiling point (64-65°C). The reaction was complete after 1.5-2 h and proceeded under mild conditions without added catalyst. This helped to retain the labile ester group [13].



3a - z, 4a - j

3a - z: R = Me; **4a - j:** R = Et

3a: R_1 = H; **3b:** C(O)Me; **3c:** C(O)Et; **3d:** C(O)Pr-*n*; **3e:** C(O)Pr-*n*; **3f:** $C(O)(CH_2)_6Me$; **3g:** $C(O)(CH_2)_8Me$; **3h:** $C(O)(CH_2)_{11}Me$; **3i:** $C(O)(CH_2)_{16}Me$; **3j:** $C(O)CH=CH_2$; **3k:** $C(O)CMe=CH_2$; **3l:** $C(O)(CH_2)_7CH=CH(CH_2)_7Me$-*cis*; **3m:** $C(O)CH_2C_6H_5$; **3n:** $C(O)CH_2CHMeC_6H_5$; **3o:** $C(O)(CH_2)_2OC_6H_4Me$-4; **3p:** $C(O)C_6H_5$; **3q:** $C(O)C_6H_4Me$-4; **3r:** $C(O)C_6H_5Cl$-2; **3s:** $C(O)C_6H_4Cl$-4; **3t:** $C(O)C_6H_3Cl_2$-2,4; **3u:** $C(O)CH_2OC_6H_3Cl_2$-2,4; **3v:** $C(O)CH_2Br$; **3w:** $C(O)CHBrCHBrC_6H_5$; **3x:** $C(O)C_6H_4Br$-4; **3y:** $C(O)C_6H_4NO_2$-3; **3z:** ½ $[(O)C(CH_2)_2C(O)]$; **4a:** R_1 = H; **4b:** C(O)Me; **4c:** C(O)Et; **4d:** C(O)Pr-*n*; **4e:** C(O)Pr-*i*; **4f:** $C(O)CH_2CHMe$; **4g:** $C(O)C_6H_5$; **4h:** $C(O)C_6H_4Me$-4; **4i:** $C(O)C_6H_4Cl$-2; **4j:** ½ $[(O)C(CH_2)_2C(O)]$

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TABLE 1. Antitumor Activity of Azomethines **3a-z** and **4a-j** *in vitro* [compound concentration (mmol/L) effecting complete suppression of tumor-cell growth]

Compound	Tumor type				
	I	II	III	IV	V
3a	>10	>10	>10	>10	>10
3b	8	10	9	9	10
3c	8	9	10	9	9
3d	7	9	8	7	8
3e	8	8	7	9	10
3f	6	10	9	8	8
3g	6	8	7	8	7
3h	6	7	8	10	8
3i	6	7	9	8	8
3j	7	8	8	8	8
3k	7	8	7	8	9
3l	6	6	8	7	8
3m	4	7	7	8	9
3n	4	7	6	8	7
3o	3	6	5	6	6
3p	4	6	6	7	8
3q	3	5	5	8	6
3r	2	5	4	6	6
3s	2	5	7	6	6
3t	1	4	7	5	5
3u	0.8	4	3	4	4
3v	0.7	3	4	3	4
3w	1	3	4	4	4
3x	0.3	4	3	3	5
3y	0.2	3	4	3	4
3z	4	7	7	9	7
4a	9	10	10	9	10
4b	6	6	8	8	7
4c	6	7	8	7	8
4d	5	6	6	6	6
4e	6	7	8	8	8
4f	5	7	7	7	8
4g	3	6	6	7	7
4h	2	5	4	7	5
4i	1	3	3	4	4
4j	3	5	6	8	6

Starting compounds **1** and **2** were converted into the corresponding azomethines **3a-z** and **4a-j** in quantitative yields of 90-94%. It was expected that **3a-z** and **4a-j** would be promising for studies of their biological activities and the preparation of optical materials based on them [14].

The structures of the synthesized azomethines were confirmed by elemental analysis and PMR, IR, and UV spectra.

The UV spectra of **3a-d**, **3i**, and **4a-d** contain absorption bands at 220, 254, and 323-325 nm; of **3e-h**, **3q**, **3s**, **4e**, **4f**, and **4h** (λ_{max}, nm): 220-223, 253-255, 310-314, and 334-336; of **3j-l**, **3o**, **3t**, and **3y**: 206-208, 220, 253-255, and 324-326; of **3m**, **3n**, **3r**, **3s**, **3u**, **3x**, **3z**, **4i**, and **4j**: 206-208, 220, 253-255, 310-314, and 335; of **3p** and **4g**: 207, 220, 240, 254, and 323.

According to PMR spectroscopy, the prepared azomethines are mixtures of the *E*- and *Z*=isomers in a 3:2 ratio. The purity of the compounds is 98 ± 1%. The PMR spectra of the azomethines contain signals characteristic of the HC=N proton as two singlets near 8.0 ppm. The chemical shift of the proton in the minor *Z*-isomer is usually found at weaker field by about 0.2 ppm owing to deshielding by the benzene ring of the amino-acid part of the molecule [15].

We confirmed the molecular structures of **3a-z** and **4a-j** using quantum-chemical calculations of the heats of formation (H_f) of the *E*- and *Z*-isomers of **3a**, **3b**, **3p**, **3x**, **4a**, **4b**, and **4g** by an MNDO-PM-3 semiempirical approximation [16] using the GAMESS program [17]. All bond lengths and bond and dihedral angles were fully optimized. The calculations gave the following values (H_f, kcal/mol) for the *E*-isomers: -100.0, **3a**; -135.5, **3b**; -99.3, **3p**; -91.3, **3x**; -106.7, **4a**; -141.3, **4b**; -105.7, **4g**; for the *Z*-isomers: -99.7, **3a**; -134.8, **3b**; -99.0, **3p**; -90.8, **3x**; -104.6, **4a**; -139.3, **4b**; -104.6, **4g**.

Quantum-chemical calculations demonstrated that the *E*-configuration (attributed quantitatively to the predominant isomer) is energetically more favored than the *Z*-configuration by 0.3-2.1 kcal/mol. These calculations agree well with those reported in the literature for related compounds [13, 18].

The antitumor activities of the synthesized azomethines were studied for five types of cancer in various cell cultures: leukemia (I), melanoma (II), colon cancer (III), kidney (IV), and breast (V) (Table 1). Compounds **3a-z** and **4a-j** were tested *in vitro* after a preliminary computer analysis using a structure—activity program.

The studied azomethines exhibited the greatest cytostatic activity for leukemia (I). It should be noted that introducing aromatic, Cl-, Br-, and NO_2-containing constituents into the azomethines produced a significant increase in the activity for all five types of cancer. Azomethines based on vanillal (**4a-j**) that contain an EtO group were more active than analogous compounds based on vanillin with a MeO group (**3a-z**). The least active compounds contained hydroxyl (**3a** and **4a**).

EXPERIMENTAL

IR spectra were recorded on a Protege-460 (Nicolet) IR-Fourier spectrophotometer in KBr disks; UV spectra, on a Specord UV-Vis instrument using $1 \cdot 10^{-4}$ M solutions in methanol.

PMR spectra were obtained on a BS-587A spectrometer (100 MHz, Tesla) using 5% solutions in $(CD_3)_2SO$. Chemical shifts were determined relative to octamethyltetracyclosiloxane as internal standard. Esters of vanillin and vanillal **2** were synthesized as before [19].

4-Hydroxy(alkyloyloxy, aryloyloxy)-3-methoxy(ethoxy)phenylmethylen-(2-carboxyphenyl)amines 3a-z and 4a-j (Schiff bases) (general method). Vanillin, vanillal, or their ester **2** (0.01 mol) was dissolved in absolute methanol (50-100 mL) and treated with 2-aminobenzoic acid **1** (0.01 mol; for **3y** and **4j**, 0.02 mol was used). The resulting solution was refluxed for 1.5-2 h and left for 20-30 h at 20-23°C. The resulting solid of **3a-z** and **4a-j** was filtered on a porous glass filter, washed with a small amount of methanol, and dried in vacuo. The products **3a-z** and **4a-j** were sufficiently pure and, therefore, were not recrystallized. The used methanol could be regenerated by fractional distillation.

Elemental analyses of all compounds agreed with those calculated.

This method produced:

4-Hydroxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3a). Yield 91%, mp 172-173°C, $C_{15}H_{13}NO_4$. IR spectrum (ν, cm^{-1}): 1800-3550 (OH); 3090, 3070, 3040, 3010 (=CH and CH_{Ar}); 2957, 2924, 2853 (CH_{Alk}); 1690 (C=O); 1623 (C=N); 1600, 1590, 1513, 1465, 1452, 1426, 1390, 1370 (Ar); 1305, 1280, 1260, 1209, 1156, 1126, 1090, 1030 (C–O); 847, 815, 800, 760, 755, 690, 660, 650, 610 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.87 (CH_3, s), 6.30-7.74 (C_6H_3 and C_6H_4, m), 7.90 and 8.00 (HC=N, s and s), 9.75 (CO_2H, s).

4-Acetyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3b). Yield 93%, mp 166-167°C, $C_{17}H_{15}NO_5$. IR spectrum (ν, cm^{-1}): 2030-1650 (OH); 3090, 3080, 3065, 3030, 3010 (=CH and CH_{Ar}); 2960, 2940, 2922, 2880, 2840, 2830 (CH_{Alk}); 1757, 1706 (C=O); 1623 (C=N); 1592, 1505, 1466, 1449, 1421, 1397, 1374 (Ar); 1281, 1220, 1199, 1156, 1125, 1030, 1015 (C–O); 847, 830, 790, 770, 755, 720, 693, 680, 640, 615 (CH_{Ar}).

PMR spectrum (δ, ppm): 2.27 [$CH_3C(O)$, s], 3.88 (CH_3, s), 6.30-7.75 (C_6H_3 and C_6H_4, m), 8.10 and 8.20 (HC=N, s and s), 9.95 (CO_2H, s).

4-Propionyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3c). Yield 90%, mp 105-106°C, $C_{18}H_{17}NO_5$. IR spectrum (ν, cm^{-1}): 2050-3620 (OH); 3080, 3064, 3040, 3015 (=CH and CH_{Ar}); 2980, 2941, 2883, 2831 (CH_{Alk}); 1762, 1695

(C=O); 1622 (C=N); 1591, 1507, 1464, 1421, 1397, 1354 (Ar); 1320, 1287, 1242, 1201, 1154, 1121, 1075, 1056, 1033, 991 (C–O); 888, 860, 847, 830, 800, 785, 762, 750, 693, 650, 640, 630, 615 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.28 (CH_3, t), 2.55 (CH_2, q), 3.88 (CH_3O, s), 6.30-7.75 (C_6H_3 and C_6H_4, m), 8.10 and 8.20 (HC=N, s and s), 9.94 (CO_2H, s).

4-*p*-Butyryloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3d). Yield 90%, mp 112-113°C, $C_{19}H_{19}NO_5$. IR spectrum (ν, cm^{-1}): 2030-3650 (OH); 3085, 3070, 3040, 3010 (=CH and CH_{Ar}); 2990, 2956, 2932, 2880, 2850, 2835 (CH_{Alk}); 1763, 1707 (C=O); 1628 (C=N); 1600, 1590, 1508, 1455, 1422, 1410, 1390, 1381 (Ar); 1281, 1242, 1203, 1158, 1137, 1124, 1099, 1054, 1032, 1003, 995 (C–O); 846, 840, 803, 775, 750, 698, 660, 630, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.04 (CH_3, t), 1.65 (CH_2, m), 2.55 (CH_2, t), 3.88 (CH_3O, s), 6.30-7.80 (C_6H_3 and C_6H_4, m), 8.10 and 8.20 (HC=N, s and s), 9.96 (CO_2H, s).

4-*i*-Butyryloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3e). Yield 91%, mp 126-127°C, $C_{19}H_{19}NO_5$. IR spectrum (ν, cm^{-1}): 2100-3650 (OH); 3080, 3070, 3035, 3020 (=CH and CH_{Ar}); 2970, 2939, 2875, 2854, 2840 (CH_{Alk}); 1755, 1705 (C=O); 1624 (C=N); 1597, 1506, 1466, 1450, 1421, 1398, 1380 (Ar); 1282, 1242, 1220, 1202, 1183, 1157, 1127, 1096, 1030, 1004, 975 (C–O); 861, 848, 819, 790, 775, 762, 743, 693, 650, 616 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.34 [$(CH_3)_2C$, d], 2.81 (CH, m), 3.89 (CH_3, s), 6.40-7.90 (C_6H_3 and C_6H_4, m), 8.12 and 8.25 (HC=N, s and s), 9.96 (CO_2H, s).

4-*n*-Capryloyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3f). Yield 94%, mp 65-66°C, $C_{23}H_{27}NO_5$. IR spectrum (ν, cm^{-1}): 2100-3650 (OH); 3085, 3074, 3045, 3015 (=CH and CH_{Ar}); 2955, 2930, 2856 (CH_{Alk}); 1757, 1698 (C=O); 1619 (C=N); 1594, 1508, 1488, 1465, 1421, 1378 (Ar); 1323, 1278, 1253, 1243, 1200, 1156, 1145, 1122, 1101, 1056, 1032, 995 (C–O); 870, 845, 830, 803, 780, 756, 740, 695, 655, 640, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.94 (CH_3, t), 1.35 [$(CH_2)_4$, m], 1.82 (CH_2, m), 2.60 (CH_2, m), 3.89 (CH_3O, s), 6.40-7.88 (C_6H_3 and C_6H_4, m), 8.12 and 8.24 (HC=N, s and s), 9.95 (CO_2H, s).

4-*n*-Caprinoyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3g). Yield 93%, mp 105-106°C, $C_{25}H_{31}NO_5$. IR spectrum (ν, cm^{-1}): 2030-3620 (OH); 3080, 3060, 3040, 3010 (=CH and CH_{Ar}); 2954, 2924, 2853 (CH_{Alk}); 1753, 1699 (C=O); 1622 (C=N); 1596, 1507, 1466, 1450, 1420, 1397, 1377 (Ar); 1320, 1279, 1242, 1197, 1155, 1121, 1102, 1056, 1031, 999 (C–O); 860, 848, 835, 790, 762, 745, 725, 695, 660, 635, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.89 (CH_3, t), 1.22-1.60 [$(CH_2)_6$, m], 1.84 (CH_2, t), 2.64 (CH_2, t), 3.89 (CH_3O, s), 6.40-7.90 (C_6H_3 and C_6H_4, m), 8.12 and 8.26 (HC=N, s and s), 9.95 (CO_2H, s).

4-*n*-Tridecanoyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3h). Yield 90%, mp 97-98°C, $C_{28}H_{37}NO_5$. IR spectrum (ν, cm^{-1}): 2100-3640 (OH); 3080, 3065, 3040, 3020, 3010 (=CH and CH_{Ar}); 2955, 2922, 2852 (CH_{Alk}); 1748, 1706 (C=O); 1623 (C=N); 1596, 1507, 1466, 1453, 1421, 1398, 1380 (Ar); 1320, 1282, 1240, 1220, 1198, 1155, 1123, 1110, 1060, 1028, 1003 (C–O); 860, 852, 840, 790, 762, 746, 720, 695, 655, 640, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.90 (CH_3, t), 1.18-1.68 [$(CH_2)_9$, m], 1.78 (CH_2, m), 2.64 (CH_2, m), 3.88 (CH_3O, s), 6.45-8.02 (C_6H_3 and C_6H_4, m), 8.10 and 8.25 (HC=N, s and s), 9.94 (CO_2H, s).

4-*n*-Stearoyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3i). Yield 90%, mp 63-64°C, $C_{33}H_{47}NO_5$. IR spectrum (ν, cm^{-1}): 2120-3660 (OH); 3090, 3080, 3070, 3040, 3007 (=CH and CH_{Ar}); 2960, 2917, 2850 (CH_{Alk}); 1762, 1704 (C=O); 1624 (C=N); 1597, 1507, 1471, 1421, 1400, 1379, 1354 (Ar); 1313, 1281, 1241, 1220, 1199, 1155, 1122, 1101, 1056, 1032, 1000 (C–O); 860, 845, 835, 800, 790, 762, 719, 693, 640, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.90 (CH_3, t), 1.10-2.12 [$(CH_2)_{15}$, m], 2.72 (CH_2, t), 3.88 (CH_3O, s), 6.45-8.04 (C_6H_3 and C_6H_4, m), 8.10 and 8.24 (HC=N, s and s), 9.95 (CO_2H, s).

4-Acryloyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3j). Yield 91%, mp 103-104°C, $C_{18}H_{15}NO_5$. IR spectrum (ν, cm^{-1}): 2050-3650 (OH); 3080, 3070, 3040, 3015 (=CH and CH_{Ar}); 2960, 2940, 2920, 2880, 2855, 2830 (CH_{Alk}); 1753, 1704 (C=O); 1623 (C=N); 1592, 1505, 1463, 1451, 1421, 1397, 1362 (Ar); 1320, 1281, 1241, 1215, 1200, 1160, 1140, 1122, 1028, 1001 (C–O); 848, 830, 810, 800, 790, 761, 743, 725, 692, 635, 617 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.89 (CH_3O, s), 5.85-6.90 (CH=CH_2, m), 6.40-8.00 (C_6H_3 and C_6H_4, m), 8.12 and 8.26 (HC=N, s and s), 9.94 (CO_2H, s).

4-Metacryloyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3k). Yield 90%, mp 140-141°C, $C_{19}H_{17}NO_5$. IR spectrum (ν, cm^{-1}): 2060-3650 (OH); 3090, 3080, 3070, 3040, 3010 (=CH and CH_{Ar}); 2985, 2960, 2940, 2920, 2890, 2860, 2830 (CH_{Alk}); 1734, 1706 (C=O); 1623 (C=N); 1594, 1506, 1466, 1450, 1421, 1397, 1380 (Ar); 1319, 1282, 1241, 1220, 1203, 1159, 1138, 1029, 1003 (C–O); 870, 846, 825, 803, 785, 762, 745, 725, 692, 650, 640, 618 (CH_{Ar}).

PMR spectrum (δ, ppm): 2.12 (CH_3, t), 3.89 (CH_3O, s), 5.80 (=CH, t), 6.42 (=CH, t), 6.40-8.02 (C_6H_3 and C_6H_4, m), 8.10 and 8.24 (HC=N, s and s), 9.95 (CO_2H, s).

4-Oleyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3l). Yield 90%, mp 40-41°C, $C_{33}H_{45}NO_5$. IR spectrum (ν, cm^{-1}): 2130-3700 (OH); 3080, 3064, 3006 (=CH and CH_{Ar}); 2955, 2925, 2853 (CH_{Alk}); 1755, 1700 (C=O); 1623 (C=N); 1596, 1562, 1507, 1466, 1421, 1399, 1377 (Ar); 1319, 1279, 1242, 1200, 1157, 1123, 1057, 1032 (C–O); 860, 849, 830, 762, 752, 730, 723, 694, 660, 622 (CH_{Ar}).

PMR spectrum (δ, ppm): 0.90 (CH_3, t), 1.10-2.20 [$(CH_2)_5$ and $(CH_2)_6$, m], 2.58 (CH_2, t), 3.88 (CH_3O, s), 5.38 (=CH, t), 5.42 (=CH, t), 6.42-8.02 (C_6H_3 and C_6H_4, m), 8.12 and 8.26 (HC=N, s and s), 9.94 (CO_2H, s).

4-Phenylacetyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3m). Yield 91%, mp 107-108°C, $C_{23}H_{19}NO_5$. IR spectrum (ν, cm^{-1}): 2020-3640 (OH); 3090, 3064, 3030, 3005 (=CH and CH_{Ar}); 2960, 2940, 2920, 2884, 2840, 2831 (CH_{Alk}); 1752, 1704 (C=O); 1623 (C=N); 1593, 1505, 1465, 1453, 1421, 1397 (Ar); 1281, 1238, 1200, 1156, 1123, 1074, 1029, 1003 (C–O); 847, 829, 790, 761, 750, 725, 717, 692, 660, 630, 616 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.80 (CH_2, s), 0.89 (CH_3, s), 6.40-8.00 (C_6H_3, C_6H_4, and C_6H_5, m), 8.10 and 8.20 (HC=N, s and s), 9.95 (CO_2H, s).

4-(2-Phenyl-*n*-butyryloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3n). Yield 92%, mp 41-42°C, $C_{25}H_{23}NO_5$. IR spectrum (ν, cm^{-1}): 2170-3680 (OH); 3080, 3062, 3028, 3003 (=CH and CH_{Ar}); 2966, 2938, 2874, 2836 (CH_{Alk}); 1760, 1698 (C=O); 1619 (C=N); 1601, 1590, 1561, 1504, 1465, 1454, 1421, 1381 (Ar); 1323, 1275, 1241, 1201, 1156, 1121, 1082, 1064, 1032 (C–O); 863, 836, 762, 734, 701, 642, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.42 (CH_3, d), 2.90 (CH_2, d), 3.42 (CH, q), 3.88 (CH_3O, s), 6.40-8.06 (C_6H_3, C_6H_4, and C_6H_5, m), 8.10 and 8.22 (HC=N, s and s), 9.96 (CO_2H, s).

4-[2-(4-Toluyloxy)-propionyloxy]-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3o). Yield 93%, mp 64-65°C, $C_{25}H_{23}NO_6$. IR spectrum (ν, cm^{-1}): 2200-3700 (OH); 3080, 3060, 3040, 3003 (=CH and CH_{Ar}); 2990, 2980, 2955, 2924, 2890, 2854, 2823 (CH_{Alk}); 1766, 1700 (C=O); 1612 (C=N); 1590, 1512, 1467, 1457, 1414, 1392, 1360, 1340 (Ar); 1320, 1294, 1278, 1248, 1212, 1195, 1154, 1103, 1051, 1032, 997 (C–O); 886, 864, 815, 809, 790, 750, 740, 702, 695, 660, 615 (CH_{Ar}).

PMR spectrum (δ, ppm): 2.30 (CH_3, s), 3.10 (CH_2O, t), 3.89 (CH_3O, s), 4.42 [$CH_2C(O)$, t], 6.40-8.08 (C_6H_3 and $2\times C_6H_4$, m), 8.08 and 8.18 (HC=N, s and s), 9.96 (CO_2H, s).

4-Benzoyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3p). Yield 92%, mp 207-208°C, $C_{22}H_{17}NO_5$. IR spectrum (ν, cm^{-1}): 2030-3650 (OH); 3085, 3070, 3030, 3005 (=CH and CH_{Ar}); 2970, 2945, 2922, 2880, 2840, 2830 (CH_{Alk}); 1752, 1708 (C=O); 1625 (C=N); 1592, 1572, 1507, 1465, 1449, 1430, 1421, 1399 (Ar); 1285, 1247, 1199, 1157, 1124, 1097, 1029, 1004, 980 (C–O); 880, 840, 820, 810, 790, 770, 741, 713, 692, 660, 640, 622 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.91 (CH_3, s), 6.34-7.75 (C_6H_3, C_6H_4, and C_6H_5), 8.04 and 8.12 (HC=N, s and s), 9.97 (CO_2H, s).

4-(4-Methylbenzoyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3q). Yield 90%, mp 182-183°C, $C_{23}H_{19}NO_5$. IR spectrum (ν, cm^{-1}): 2000-3650 (OH); 3074, 3040, 3012 (=CH and CH_{Ar}); 2976, 2937, 2870, 2852 (CH_{Alk}); 1740, 1707 (C=O); 1620 (C=N); 1613, 1590, 1620, 1505, 1485, 1463, 1420, 1380 (Ar); 1318, 1300, 1261, 1222, 1199, 1179, 1158, 1118, 1059, 1029, 1018 (C–O); 890, 874, 840, 790, 746, 688, 650, 635, 620, 605 (CH_{Ar}).

PMR spectrum (δ, ppm): 2.44 (CH_3, s), 3.90 (CH_3O, s), 6.45-8.12 (C_6H_3 and $2\times C_6H_4$, m), 8.08 and 8.18 (HC=N, s and s), 9.96 (CO_2H, s).

4-(2-Chlorobenzoyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3r). Yield 93%, mp 206-207°C, $C_{22}H_{16}NClO_5$. IR spectrum (ν, cm^{-1}): 2050-3700 (OH); 3090, 3080, 3060, 3035, 3005 (=CH and CH_{Ar}); 2970, 2940, 2923, 2890, 2845, 2835 (CH_{Alk}); 1752, 1701 (C=O); 1625 (C=N); 1591, 1565, 1507, 1465, 1449, 1430, 1421, 1398 (Ar); 1320, 1284, 1270, 1245, 1220, 1199, 1156, 1124, 1096, 1029, 1005, 980 (C–O); 880, 845, 820, 810, 790, 760, 741, 710, 690, 645, 630, 620, 590 (CH_{Ar}), 550 (C–Cl).

PMR spectrum (δ, ppm): 3.91 (CH_3, s), 6.42-8.15 (C_6H_3 and $2\times C_6H_4$, m), 8.14 and 8.26 (HC=N, s and s), 10.02 (CO_2H, s).

4-(4-Chlorobenzoyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3s). Yield 91%, mp 192-193°C, $C_{22}H_{16}NClO_5$. IR spectrum (ν, cm^{-1}): 2050-3630 (OH); 3090, 3080, 3070, 3040, 3025, 3005 (=CH and CH_{Ar}); 2965, 2940, 2925, 2890, 2855, 2825 (CH_{Alk}); 1740, 1705 (C=O); 1623 (C=N); 1592, 1506, 1485, 1466, 1445, 1421, 1399 (Ar); 1315, 1284, 1261, 1201, 1156, 1127, 1091, 1070, 1029, 1014 (C–O); 869, 843, 822, 762, 749, 692, 678, 665, 640, 619, 592 (CH_{Ar}), 550 (C–Cl).

PMR spectrum (δ, ppm): 3.91 (CH_3, s), 6.45-8.18 (C_6H_3 and 2×C_6H_4, m), 8.20 and 8.30 (HC=N, s and s), 10.04 (CO_2H, s).

4-(2,4-Dichlorobenzoyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3t). Yield 92%, mp 235-236°C, $C_{22}H_{15}NCl_2O_5$. IR spectrum (ν, cm^{-1}): 2050-3650 (OH); 3095, 3080, 3060, 3035 (=CH and CH_{Ar}); 2960, 2923, 2855, 2820 (CH_{Alk}); 1751, 1708 (C=O); 1625 (C=N); 1590, 1470, 1507, 1465, 1449, 1421, 1400, 1380 (Ar); 1283, 1265, 1237, 1200, 1157, 1149, 1126, 1087, 1029, 1003 (C–O); 880, 862, 845, 823, 800, 770, 760, 745, 720, 692, 680, 635, 620 (CH_{Ar}); 560, 550 (C–Cl).

PMR spectrum (δ, ppm): 3.91 (CH_3, s), 6.42-8.10 (2×C_6H_3 and C_6H_4, m), 8.20 and 8.30 (HC=N, s and s), 10.02 (CO_2H, s).

4-(2,4-Dichlorophenoxyacetyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3u). Yield 94%, mp 93-94°C, $C_{23}H_{17}NCl_2O_6$. IR spectrum (ν, cm^{-1}): 2300-3610 (OH); 3100, 3080, 3040, 3010 (=CH and CH_{Ar}); 2990, 2955, 2924, 2853, 2830 (CH_{Alk}); 1779, 1702 (C=O); 1623 (C=N); 1609, 1585, 1508, 1480, 1414, 1390, 1380, 1350 (Ar); 1305, 1275, 1265, 1240, 1198, 1172, 1152, 1119, 1105, 1083, 1048, 1034, 994 (C–O); 875, 860, 840, 805, 785, 760, 715, 700, 670, 640 (CH_{Ar}), 555 (C–Cl).

PMR spectrum (δ, ppm): 3.90 (CH_3, s), 5.00 (CH_2, s), 6.40-8.08 (2×C_6H_3 and C_6H_4, m), 8.22 and 8.32 (HC=N, s and s), 10.00 (CO_2H, s).

4-Bromoacetyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3v). Yield 90%, mp 96-97°C, $C_{17}H_{14}NBrO_5$. IR spectrum (ν, cm^{-1}): 2200-3650 (OH); 3090, 3060, 3047, 3020, 3002 (=CH and CH_{Ar}); 2962, 2939, 2920, 2843, 2805 (CH_{Alk}); 1769, 1690 (C=O); 1627 (C=N); 1587, 1516, 1466, 1455, 1433, 1408 (Ar); 1297, 1269, 1234, 1217, 1180, 1160, 1128, 1029 (C–O); 870, 850, 823, 785, 754, 730, 690, 680, 640, 625 (CH_{Ar}); 555 (C–Br).

PMR spectrum (δ, ppm): 3.90 (CH_3, s), 4.39 (CH_2, s), 6.40-7.92 (C_6H_3 and C_6H_4, m), 8.12 and 8.24 (HC=N, s and s), 9.96 (CO_2H, s).

4-(1,2-Dibromo-2-phenylpropionyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3w). Yield 93%, mp 51-52°C, $C_{24}H_{19}NBr_2O_5$. IR spectrum (ν, cm^{-1}): 2250-3680 (OH); 3070, 3040, 3005 (=CH and CH_{Ar}); 2980, 2940, 2910, 2880, 2825 (CH_{Alk}); 1731, 1700 (C=O); 1504, 1464, 1450, 1420, 1378, 1350 (Ar); 1321, 1278, 1240, 1196, 1156, 1121, 1080, 1055, 1031 (C–O); 862, 830, 800, 763, 735, 694, 640, 605 (CH_{Ar}); 545, 555 (C–Br).

PMR spectrum (δ, ppm): 3.90 (CH_3, s), 4.30 (CH, d), 5.14 (CH, d), 6.50-8.02 (C_6H_3, C_6H_4, and C_6H_5, m), 8.14 and 8.24 (HC=N, s and s), 9.98 (CO_2H, s).

4-(4-Bromobenzoyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3x). Yield 94%, mp 208-209°C, $C_{22}H_{16}NBrO_5$. IR spectrum (ν, cm^{-1}): 2000-3650 (OH); 3090, 3075, 3063, 3029 (=CH and CH_{Ar}); 2965, 2937, 2890, 2860, 2831 (CH_{Alk}); 1738, 1703, 1688 (C=O); 1621 (C=N); 1590, 1560, 1505, 1486, 1466, 1451, 1420, 1397 (Ar); 1323, 1283, 1260, 1202, 1156, 1125, 1069, 1029, 1010 (C–O); 867, 845, 820, 800, 780, 747, 735, 602, 691, 677, 660, 640, 620, 595 (CH_{Ar}), 550 (C–Br).

PMR spectrum (δ, ppm): 3.90 (CH_3, s), 6.44-8.16 (C_6H_3 and 2×C_6H_4, m), 8.20 and 8.32 (HC=N, s and s), 10.04 (CO_2H, s).

4-(3-Nitrobenzoyloxy)-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3y). Yield 93%, mp 125-126°C, $C_{22}H_{16}N_2O_7$. IR spectrum (ν, cm^{-1}): 2040-3650 (OH); 3105, 3086, 3060, 3040, 3010 (=CH and CH_{Ar}); 2960, 2925, 2895, 2855, 2835, 2800 (CH_{Alk}); 1750, 1681 (C=O); 1617 (C=N); 1591, 1561, 1505, 1486, 1448, 1421 (Ar); 1531, 1352 (NO_2); 1328, 1300, 1245, 1203, 1156, 1123, 1097, 1070, 1059, 1027, 1001 (Ar); 860, 840, 820, 755, 717, 700, 657, 620 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.90 (CH_3, s), 6.45-9.12 (C_6H_3 and 2×C_6H_4, m), 8.28 and 8.38 (HC=N, s and s), 10.04 (CO_2H, s).

4-Succinoyloxy-3-methoxyphenylmethylen-(2-carboxyphenyl)amine (3z). Yield 92%, mp 222-223°C, $C_{34}H_{28}N_2O_{10}$. IR spectrum (ν, cm^{-1}): 2000-3640 (OH); 3080, 3065, 3015 (=CH and CH_{Ar}); 2970, 2940, 2884, 2845, 2831 (CH_{Alk}); 1754, 1702 (C=O); 1622 (C=N); 1592, 1505, 1489, 1465, 1450, 1420, 1397, 1365 (Ar); 1320, 1281, 1241, 1220, 1199, 1163, 1122, 1028 (C–O); 884, 855, 849, 832, 790, 754, 692, 655, 640, 620, 590 (CH_{Ar}).

PMR spectrum (δ, ppm): 3.05 [$(CH_2)_2$, s], 3.89 (2×CH_3, s), 6.40-7.90 (2×C_6H_3 and 2×C_6H_4, m), 8.10 and 8.24 (2×HC=N, s and s), 9.95 (2×CO_2H, s).

4-Hydroxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4a). Yield 93%, mp 160-161°C, $C_{16}H_{15}NO_4$. IR spectrum (ν, cm^{-1}): 2000-3620 (OH); 3082, 3060, 3032 (=CH and CH_{Ar}); 2985, 2940, 2927, 2883, 2855, 2820 (CH_{Alk}); 1698 (C=O); 1621 (C=N); 1590, 1521, 1489, 1445, 1420, 1397, 1368 (Ar); 1300, 1271, 1235, 1213, 1180, 1170, 1137, 1090, 1041 (C–O); 852, 830, 820, 772, 730, 694, 607 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.32 (CH_3, t), 4.18 (CH_2, q), 6.34-7.72 (C_6H_3 and C_6H_4, m), 7.92 and 8.02 (HC=N, s and s), 9.76 (CO_2H, s).

4-Acetyloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4b). Yield 90%, mp 143-144°C, $C_{18}H_{17}NO_5$. IR spectrum (ν, cm^{-1}): 2030-3650 (OH); 3080, 3063, 3050, 3032 (=CH and CH_{Ar}); 2977, 2960, 2931, 2920, 2882, 2854 (CH_{Alk}); 1765, 1705 (C=O); 1622 (C=N); 1589, 1580, 1506, 1435, 1395, 1372 (Ar); 1280, 1240, 1217, 1191, 1157, 1119, 1040, 1015, 1002 (C–O); 860, 836, 802, 790, 763, 750, 725, 693, 660, 640, 630, 620, 605 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.28 (CH_3, t), 2.30 (CH_3CO_2, s), 4.12 (CH_2, q), 6.30-7.74 (C_6H_3 and C_6H_4, m), 8.12 and 8.20 (HC=N, s and s), 9.94 (CO_2H, s).

4-Propionyloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4c). Yield 90%, mp 116-117°C, $C_{19}H_{19}NO_5$. IR spectrum (ν, cm^{-1}): 2020-3640 (OH); 3080, 3070, 3055, 3040, 3005 (=CH and CH_{Ar}); 2977, 2941, 2919, 2885, 2850, 2835 (CH_{Alk}); 1762, 1705 (C=O); 1622 (C=N); 1598, 1505, 1435, 1395, 1360 (Ar); 1318, 1280, 1241, 1220, 1191, 1158, 1120, 1075, 1040, 1001 (C–O); 902, 886, 853, 829, 815, 800, 790, 763, 752, 730, 693, 640, 625 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.28 (CH_3, t), 1.42 (CH_3, t), 4.14 (CH_2, q), 2.54 (CH_2, q), 6.32-7.74 (C_6H_3 and C_6H_4, m), 8.12 and 8.20 (HC=N, s and s), 9.95 (CO_2H, s). UV spectrum: 220 (41000), 255 (17000), 325 (6000).

PMR spectrum (δ, ppm): 1.28 (CH_3, t), 2.55 (CH_2, q), 3.88 (CH_3O, s), 6.30-7.75 (C_6H_3 and C_6H_4, m), 8.10 and 8.20 (HC=N, s and s), 9.94 (CO_2H, s).

4-*n*-Butylyloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4d). Yield 90%, mp 91-92°C, $C_{20}H_{21}NO_5$. IR spectrum (ν, cm^{-1}): 2020-3600 (OH); 3080, 3070, 3030, 3005 (=CH and CH_{Ar}); 2964, 2924, 2877, 2854 (CH_{Alk}); 1758, 1705 (C=O); 1623 (C=N); 1598, 1506, 1434, 1395 (Ar); 1280, 1270, 1242, 1217, 1184, 1158, 1140, 1120, 1040, 1001 (C–O); 853, 835, 800, 795, 763, 750, 694, 655, 630, 616 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.04 (CH_3, t), 1.28 (CH_3, t), 1.65 (CH_2, m), 2.55 (CH_2, t), 4.14 (CH_2, q), 6.23-7.80 (C_6H_3 and C_6H_4, m), 8.12 and 8.20 (HC=N, s and s), 9.96 (CO_2H, s).

4-*i*-Butyryloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4e). Yield 90%, mp 87-88°C, $C_{20}H_{21}NO_5$. IR spectrum (ν, cm^{-1}): 2150-3700 (OH); 3072, 3040, 3005 (=CH and CH_{Ar}); 2979, 2937, 2900, 2878 (CH_{Alk}); 1760, 1695 (C=O); 1619 (C=N); 1600, 1590, 1506, 1488, 1470, 1450, 1434, 1390, 1350 (Ar); 1320, 1293, 1270, 1242, 1200, 1185, 1161, 1121, 1094, 1041 (C–O); 865, 815, 755, 695, 650, 640, 615 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.26 (CH_3, t), 1.34 [$(CH_3)_2C$, d], 2.81 (CH, m), 2.54 (CH_2, t), 6.42-7.94 (C_6H_3 and C_6H_4, m), 8.14 and 8.25 (HC=N, s and s), 9.94 (CO_2H, s).

4-*i*-Valeroyloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4f). Yield 90%, mp 39-40°C, $C_{21}H_{23}NO_5$. IR spectrum (ν, cm^{-1}): 2150-3700 (OH); 3070, 3035, 3005 (=CH and CH_{Ar}); 2980, 2963, 2935, 2900, 2874 (CH_{Alk}); 1760, 1697 (C–O); 1620 (C=N); 1599, 1590, 1562, 1505, 1488, 1434, 1392, 1370 (Ar); 1321, 1291, 1272, 1243, 1218, 1159, 1120, 1094, 1041, 970 (C–O); 850, 830, 785, 755, 695, 650, 640, 620, 590 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.14 [$(CH_3)_2C$, d], 1.28 (CH_3, t), 1.44-2.95 (CH and CH_2, m), 4.12 (CH_2, q), 6.40-7.90 (C_6H_3 and C_6H_4, m), 8.12 and 8.24 (HC=N, s and s), 9.94 (CO_2H, s).

4-Benzoyloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4g). Yield 90%, mp 110-111°C, $C_{23}H_{19}NO_5$. IR spectrum (ν, cm^{-1}): 2200-3680 (OH); 3070, 3035, 3004 (=CH and CH_{Ar}); 2982, 2937, 2901, 2831 (CH_{Alk}); 1743, 1696 (C=O); 1618 (C=N); 1600, 1590, 1561, 1507, 1488, 1452, 1432, 1393, 1349 (Ar); 1315, 1262, 1199, 1161, 1120, 1079, 1060, 1024, 1001 (C–O); 868, 802, 797, 755, 708, 680, 640, 630 (CH_{Ar}). PMR spectrum (δ, ppm): 1.30 (CH_3, t), 4.20 (CH_2, q), 6.35-7.70 (C_6H_3, C_6H_4, and C_6H_5), 8.04 and 8.14 (HC=N, s and s), 9.98 (CO_2H, s).

4-(4-Methylbenzoyloxy)-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4h). Yield 91%, mp 168-169°C, $C_{24}H_{21}NO_5$. IR spectrum (ν, cm^{-1}): 2100-3660 (OH); 3090, 3070, 3040, 3007 (=CH and CH_{Ar}); 2980, 2960, 2923, 2900, 2840, 2830 (CH_{Alk}); 1736, 1695 (C=O); 1621 (C=N); 1597, 1570, 1505, 1485, 1430, 1420, 1395 (Ar); 1320, 1280, 1262, 1197, 1185, 1161, 1121, 1100, 1063, 1020 (C–O); 880, 860, 830, 795, 780, 760, 745, 690, 669, 650, 640, 630, 605 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.30 (CH_3, t), 2.44 (CH_3, s), 4.20 (CH_2, q), 6.44-8.10 (C_6H_3 and 2×C_6H_4, m), 8.10 and 8.20 (HC=N, s and s), 9.96 (CO_2H, s).

4-(2-Chlorobenzoyloxy)-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4i). Yield 94%, mp 173-174°C, $C_{23}H_{18}NClO_5$. IR spectrum (ν, cm^{-1}): 2220-3630 (OH); 3100, 3080, 3040, 3005 (=CH and CH_{Ar}); 2985, 2965, 2955, 2940, 2900, 2890, 2880, 2840, 2823 (CH_{Alk}); 1750, 1704 (C=O); 1625 (C=N); 1600, 1591, 1506, 1474, 1438, 1395, 1350 (Ar); 1320, 1285, 1275, 1248, 1215, 1194, 1158, 1127, 1095, 1060, 1036 (C–O); 878, 860, 845, 820, 810, 796, 764, 755, 737, 705, 692, 650, 630, 620 (CH_{Ar}), 545 (C–Cl).

PMR spectrum (δ, ppm): 1.28 (CH_3, t), 4.22 (CH_2, q), 6.40-8.14 (C_6H_3 and 2×C_6H_4, m), 8.14 and 8.24 (HC=N, s and s), 10.04 (CO_2H, s).

4-Succinoyloxy-3-ethoxyphenylmethylen-(2-carboxyphenyl)amine (4j). Yield 93%, mp 231-232°C, $C_{36}H_{32}N_2O_{10}$. IR spectrum (ν, cm^{-1}): 2030-3650 (OH); 3066, 3055, 3033, 3007 (=CH and CH_{Ar}); 2977, 2923, 2883, 2830 (CH_{Alk}); 1758, 1697 (C=O); 1620 (C=N); 1590, 1504, 1434, 1395, 1371 (Ar); 1316, 1280, 1263, 1240, 1217, 1193, 1160, 1118, 1037, 999 (C–O); 854, 840, 812, 798, 752, 729, 692, 669, 660, 635, 614 (CH_{Ar}).

PMR spectrum (δ, ppm): 1.26 (2×CH_3, t), 3.04 [$(CH_2)_2$, s], 4.20 (2×CH_2, q), 6.42-7.94 (2×C_6H_3 and 2×C_6H_4, m), 8.12 and 8.24 (2×HC=N, s and s), 9.94 (2×CO_2H, s).

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