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Design, synthesis and structural study of novel acetamidobenzanilide derivatives

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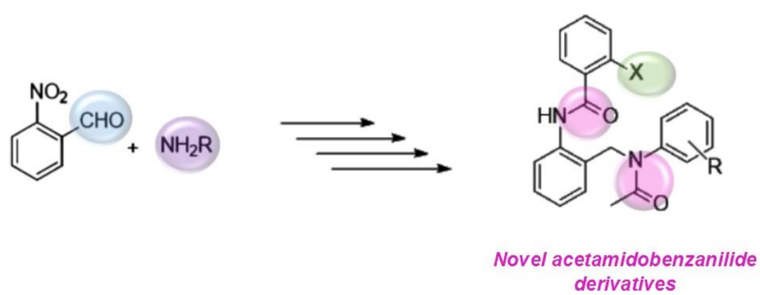
Abstract

Diamides and bisamides are compounds known for their antifungal and antitumor activities. Benzanilide derivatives, containing an acetamido moiety in particular, have not been extensively studied to-date. We present a straightforward synthesis of novel *N*-(2-[*N'*-phenyl-*N'*-acetamidomethyl])benzanilide derivatives from 2-nitrobenzaldehyde, achieved through a four-step process. The conversions were achieved in good to excellent yields, and the overall yields were deemed acceptable. These compounds were characterized by NMR spectroscopy, which revealed that several of them exhibited detectable atropisomerism.



Keywords: Acetamidobenzanilides, diamides, atropisomerism

Introduction

Diamide derivatives are compounds characterized by the presence of two carboxamide groups in their structure. Recently, they have garnered attention for their biological properties; however, studies on these compounds remain limited. Some diamide compounds have demonstrated biological activity, particularly when the amide moiety is attached to a benzene ring, as seen in benzanilides or acetanilides, or when linked to a heterocyclic group. Some of these compounds have potential applications as they may serve as insecticides,[1-2] antimicrobials,[3] anti-fungals,[4] anti-inflamatory agents[5] or anti-tumor agents.[6] Diamides have also been demonstrated to have promising bioactive properties against Chagas' disease (also known as American trypanosomiasis). This disease is a zoonosis caused by the flagellated protozoan pathogen, *Trypanosoma cruzi,*[7] and several investigations have been conducted to broaden the molecular diversity of bioactive compounds against the parasite. The trypanocidal activities of various compounds, such as acridines, phenothiazines, benzazepines, imidazoisoquinolinones, quinazolines, and pyridoquinolines, have been studied.[8-11]

In the literature, there are substances derived from amides, polyamides, and polyamines that act as inhibitors of trypanothione reductase (TryR), an enzyme exclusive to trypanosomatids or inhibitors of CAC1 cysteinyl proteinases (Figure 1).[12-16]

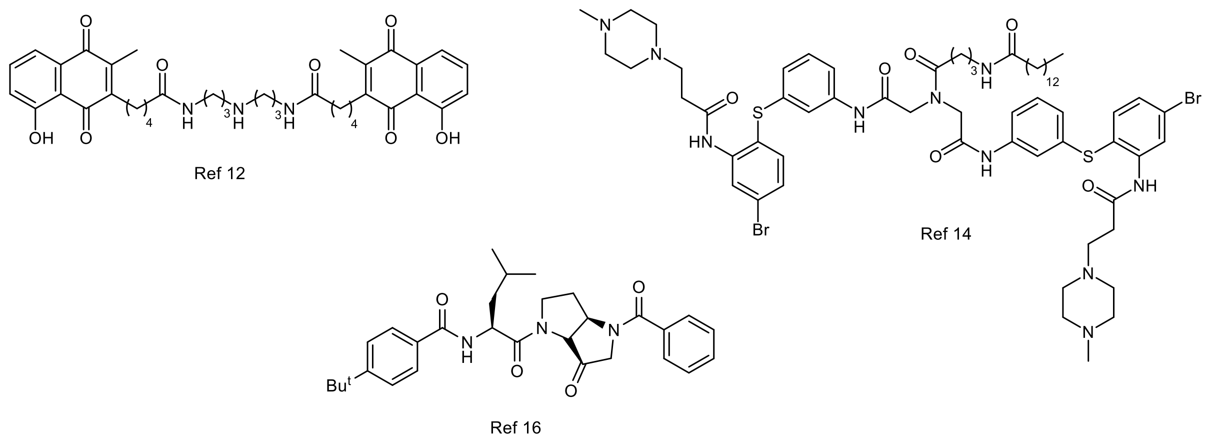


Figure 1. Trypanothione reductase and CAC1 cysteinyl proteinases inhibitors di- and polyamides.

A paradigmatic example of such compounds is suramin (Figure 2), a symmetrical polyamide approved for the treatment of *Trypanosoma brucei* infection.[17-18]

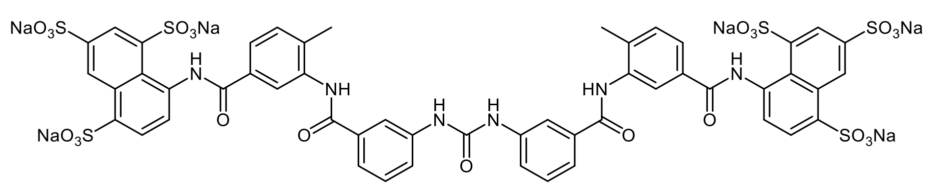


Figure 2. Suramin.

In trypanosomes, suramin inhibits several enzymes (TryR among them), interferes with the endocytosis of certain molecules, hinders the binding of LDL (low-density lipoprotein) to specific receptors, and disrupts cell division. The bioactivity of suramin at the molecular level is complex, involving multiple interactions with a variety of receptors. This is currently an issue under investigation.[19-21]

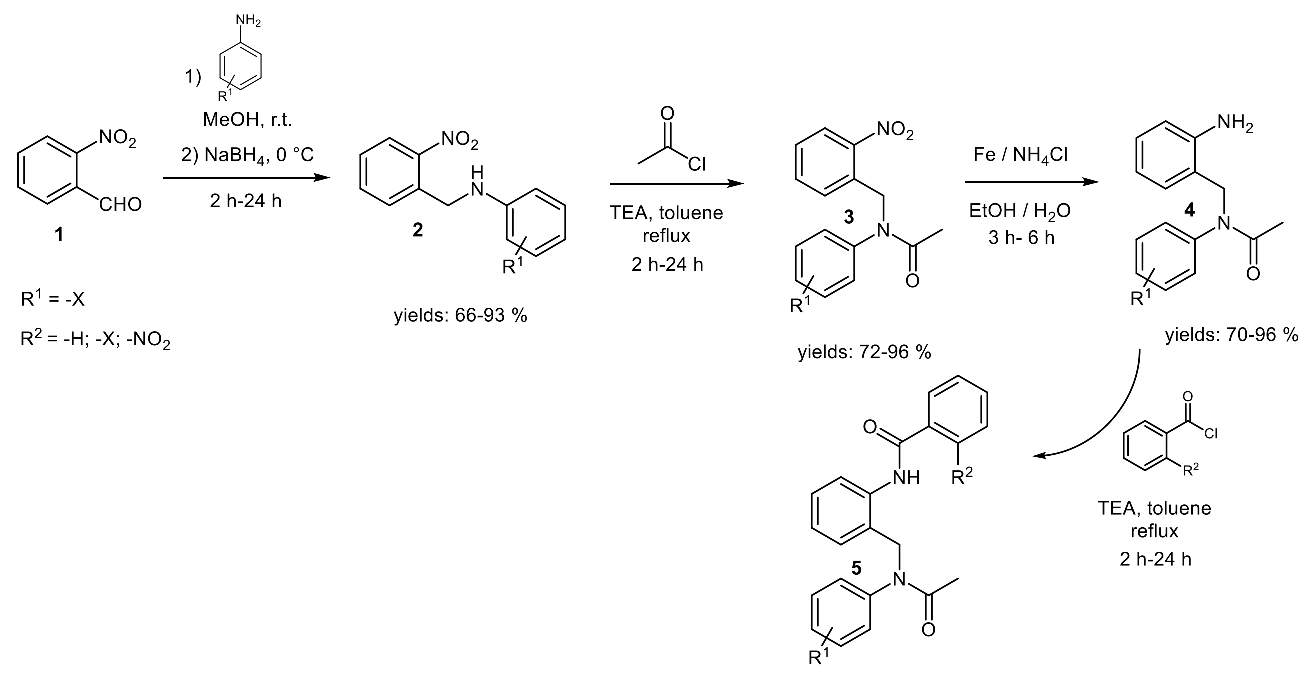
Due to the significance of suramin and other diamides or bisamides in the study of Chagas' disease, we decided to investigate the preparation and structural analysis of a series of acetamidobenzanilide derivatives as potential trypanocidal agents. Hence, we designed a synthesis strategy for preparing new *N*-(2-[*N*'-phenyl-*N*'-acetamidomethyl])benzanilide derivatives through a four-step process. The synthetic precursors employed had been previously studied in our laboratory as intermediates in the synthesis of 1,4-benzodiazepin-3-ones.[22-23]

Two structural characteristics of suramin were taken into account for the synthesis of our novel molecules: the benzanilide moiety, and another carboxamide group, in particular an acetanilide group. Through the incorporation of electron-withdrawing substituents at various positions of the benzanilide and acetanilide moieties, we have generated molecular diversity consisting of 18 analogs. Our novel molecules possess a variety of substituents with different electron-withdrawing effects and steric properties.

Results and Discussion

Synthesis

The synthetic route of these novel acetamidobenzanilides is shown in Scheme 1.

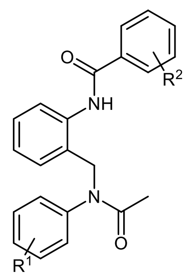


Scheme 1. Synthesis of *N*-(2-[*N*'-phenyl-*N'*-acetamidomethyl])benzanilide derivatives in a four-steps process.

In the initial step, *N*-(2-nitrobenzyl)anilines **2** were prepared by reductive amination of *o*-nitrobenzaldehyde **1** with anilines using a standard method and $NaBH_4$ as a reducing agent.[22-23] These substituted anilines were obtained in very good yields, and subsequently underwent amidation with acetyl chloride in toluene at reflux to afford the acetamides **3** in excellent yields.

In the third step of the process, the nitro group was reduced to an amino group using iron powder in a solution of ammonium chloride with ethanol-water as solvent at reflux to afford the acetamides **4**.[22-23] The final diamides **5** were obtained with a benzoylation of the amino group using benzoyl chlorides in toluene at 110 °C. Diamides **5** were prepared in good to very good yields with the exception of some compounds with $R^2=NO_2$ (**5m**, **5o** and **5r** were obtained with lower yields), and were characterized by elemental analysis, ^1H NMR, and ^{13}C NMR. Overall yields of **5** are presented in Table 1.

Table 1. Four-step overall yields of *N*-(2-[*N'*-phenyl-*N'*-acetamidomethyl])benzanilides (**5**)



	Four-step overall yield (%)
5a (R^1=*p*-Br; R^2=H)	47
5b (R^1=*o*-Cl; R^2=H)	35
5c (R^1=*p*-Cl; R^2=H)	45
5d (R^1=*o*-F; R^2=H)	37
5e (R^1=*p*-F; R^2=H)	50
5f (R^1=*p*-I; R^2=H)	22
5g (R^1=*p*-Br; R^2=*o*-Cl)	52
5h (R^1=*o*-Cl; R^2=*o*-Cl)	33
5i (R^1=*p*-Cl; R^2=*o*-Cl)	31
5j (R^1=*o*-F; R^2=*o*-Cl)	37
5k (R^1=*p*-F; R^2=*o*-Cl)	52
5l (R^1=*p*-I; R^2=*o*-Cl)	32
5m (R^1=*p*-Br; R^2=*o*-NO_2)	19
5n (R^1=*o*-Cl; R^2=*o*-NO_2)	29
5o (R^1=*p*-Cl; R^2=*o*-NO_2)	18
5p (R^1=*o*-F; R^2=*o*-NO_2)	20
5q (R^1=*p*-F; R^2=*o*-NO_2)	55
5r (R^1=*p*-I; R^2=*o*-NO_2)	15

Bioactive organic molecules interact with biological receptors in a particular and finely-tuned manner, so a thorough analysis of their structures and conformations is crucial to establishment of biological molecular mechanisms and structure-activity relationships.[24-25] In recent decades, atropisomerism has gained increased attention owing to its significance in investigations concerning natural products and bioactive molecules, as both isomers often manifest distinct pharmacological activities.[26-27]

While the conformational rigidity of bicyclic moieties is documented extensively in the literature,[28] recent interest in drug-discovery science has focused investigations of atropisomerism around the C-N axis in cases where the nitrogen atom is acyclic.[29-33] Upon analyzing the structures of the synthesized acetamidobenzanilides, we identified an atropisomeric scaffold characterized by axial chirality along the C-N bond axis, as shown in the examples illustrated in Figure 3.

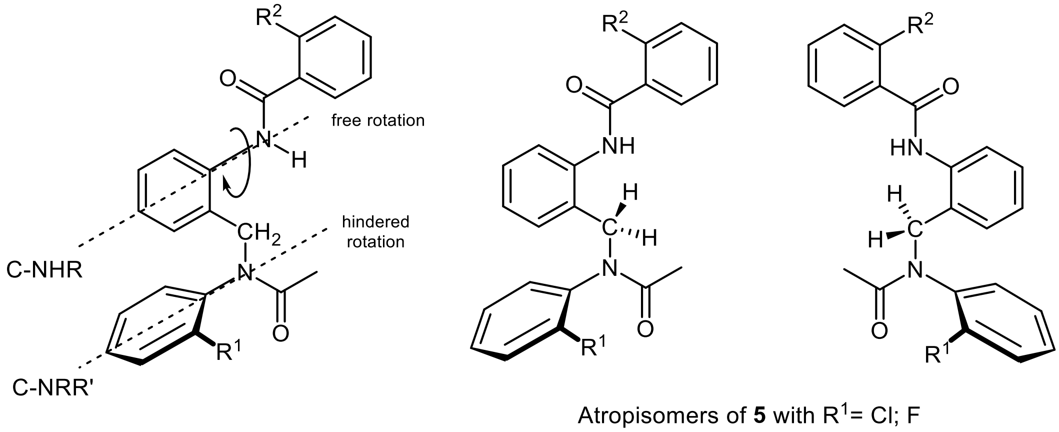


Figure 3. C-NRH and C-NRR'chiral axes and atropisomers of compounds **5.**

These benzanilides exhibit the presence of two stereogenic C-N axes, with their conformational flexibility modulated by neighboring aryl substituents. It has been previously reported that the C-NHR moiety lacks atropisomeric properties, the racemization process occurs too rapidly to be detected by ^{1}H-NMR spectroscopy.[30, 32-33] Therefore, isomerism arises from the C-NRR' axis, wherein the presence of an ortho substituent (R^1) in the second aryl group is associated with the atropisomerism, as evidenced by the distinctive pattern observed in the methylene ^{1}H NMR spectra as two diastereotopic hydrogens of the methylene group. Some of compounds **5** have shown high levels of conformational stability which generates detectable atropisomerism in all compounds with R^1 = *o*-X. In all cases, these two doublets are well resolved with $\Delta\delta$ = 0.92-0.97 ppm (J 14.7-14.8 Hz) when R^1 is Cl and $\Delta\delta$ = 0.47-0.66 ppm (J 14.6-14.8 Hz) when R^1 is F. As an example, the ^{1}H NMR of compound **5b** (R^1 = *o*-Cl) is presented in Figure 4 as well as the ^{1}H NMR of compound **5c** (R^1 = *p*-Cl) that does not exhibit atropisomerism (Figure 5).

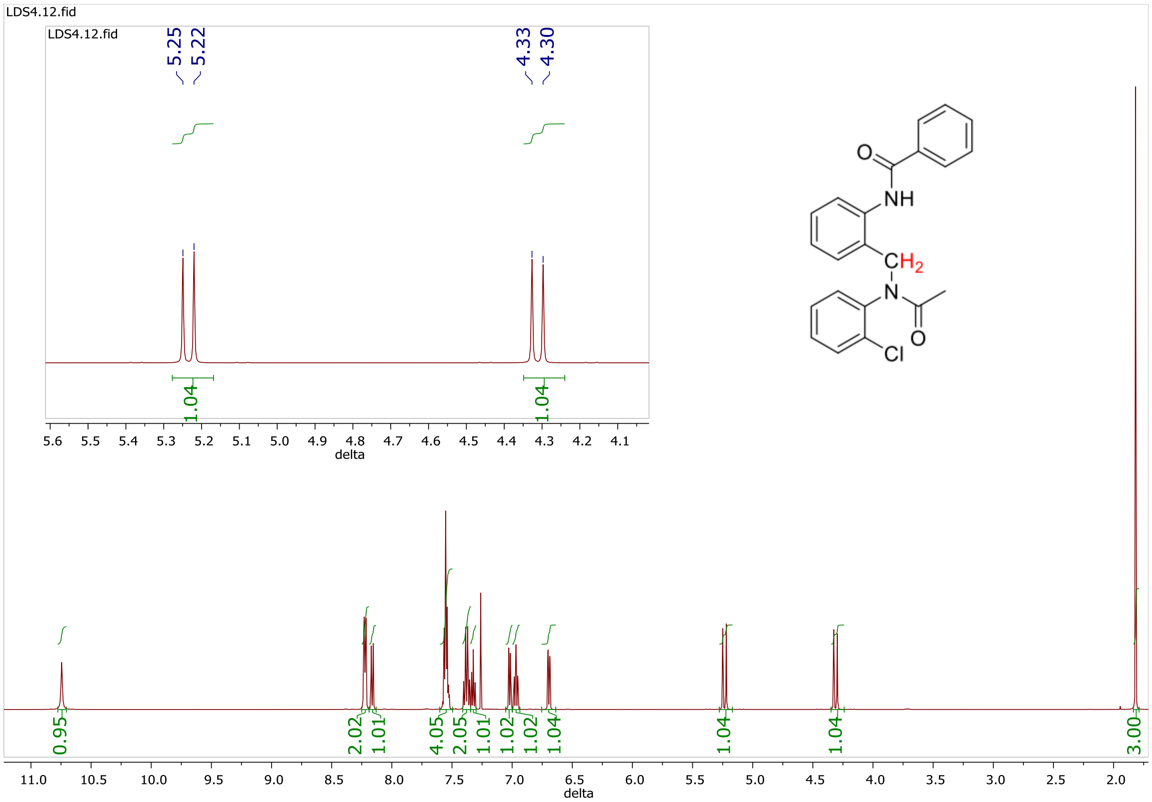


Figure 4. ^{1}H-NMR of compound **5b** showing the C**H**$_2$ signals as two doublets due to the two diastereotopic hydrogens.

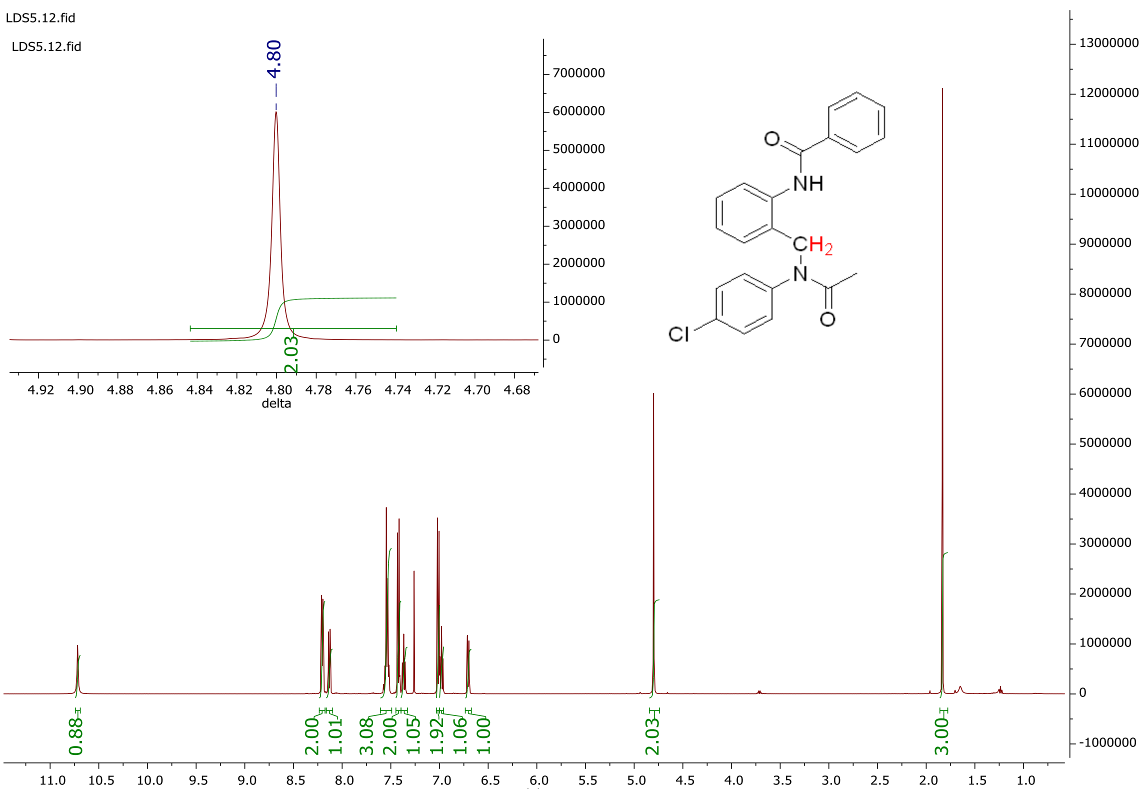


Figure 5. ^{1}H-NMR of compound **5c** showing the C**H**$_2$ signal as a singlet.

Conclusions

We have designed and implemented a facile and efficient synthesis of new *N*-(2-[*N*'-phenyl-*N*'-acetamidomethyl])benzanilide derivatives through a four-step process. All eighteen final compounds were synthesized with satisfactory yields. Their structures were confirmed by elemental analysis, ^{1}H, and ^{13}C NMR. It was observed that compounds bearing an ortho substituent (R^1) in the phenyl group of the acetanilide moeity exhibited atropisomerism attributable to the axial chirality along the C-N bond axis. The manifestation of this phenomenon was evidenced by the presence of a doublet signal in the ^{1}H NMR spectrum for each diastereotopic hydrogen within the CH_2 moiety. Some preliminary studies of biological activity against *T. cruzi* with several of these acetamidobenzanilides have been undertaken with promising early results.

Experimental Section

General. Melting points were determined with a Büchi apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Brucker Avance Neo 500, 11.75 T spectrometer operated at 500 MHz (^{1}H) and 126 MHz (^{13}C) using TMS as an internal standard. Liquid-column-chromatography separations were achieved on silica gel Grace Davison 60-200 mesh or Sigma-Aldrich 230-400 mesh. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 sheets (Merck). Elemental analyses for C, H, N, and S were performed using a Carlo Erba EA 1108 analyzer. *o*-Nitrobenzaldehyde, anilines, acetyl chloride, benzoyl chloride, triethylamine (TEA) and sodium borohydride were purchased from Aldrich. 2-Chloro and 2-nitrobenzoyl chlorides were prepared by a standard method.[34]

Synthesis of *N*-(2-nitrobenzyl)anilines (**2**). To a solution of **1** (10 mmol) in 10 mL of methanol was added the primary aniline (10 mmol) and heated at reflux for 2 h. The mixture was cooled to 0°C and $NaBH_4$ (10 mmol) was added, stirred for 2-24 h, and evaporated. The resulting solid was dissolved in CH_2Cl_2 (10 mL), washed with water (5 mL), dried over sodium sulfate, and the solvent was removed under reduced pressure to afford the *N*-(2-nitrobenzyl)anilines which were used without further purification.

Synthesis of *N*-phenyl-*N*-(2-nitrobenzyl)acetamides (**3**). *N*-(2-nitrobenzyl)aniline (**2**) (5 mmol) and 5 mmol of TEA were dissolved in toluene (10mL), and a solution of 5 mmol of acetyl chloride in 10 mL of toluene was added. The mixture was heated to reflux for 2-24 hs, cooled and washed with water (10 mL), HCl 10% (10 mL) and water (2 x 10mL). The solution was dried over sodium sulfate, and concentrated to dryness at reduced pressure, to obtain thecrude *N*-phenyl-*N*-(2-nitrobenzyl)acetamides (**3**) which were purified by silica gel column chromatography (hexane-EtOAc 8:2).

Synthesis of *N*-phenyl-*N*-(2-aminobenzyl)acetamides (**4**). *N*-Phenyl-*N*-(2-nitrobenzyl)acetamides (**3**) (3 mmol) were disolved in 30 mL of methanol, and 15 mmol of iron dust was added. The mixture was energetically stirred and a solution of 30 mmol of NH_4Cl in 15 mL of water was added and then heated at reflux until complete reaction. The mixture was filtered over celite, washed with methanol and the solvent removed at reduced pressure. The residue was disolved with 30 mL of CH_2Cl_2, washed with water, and the solution dried over sodium sulfate. The solvent was evaporated and the product purified by silica gel column cromatography (hexane-EtOAc 7:3) affording acetamides **4**.

Synthesis of *N*-(2-[*N*'-phenyl-*N*'-acetamidomethyl])benzanilides (**5**). *N*-Phenyl-*N*-(2-aminobenzyl)acetamides (**4**) (2 mmol) and 2 mmol of TEA were dissolved in toluene (5 mL) and a solution of 2 mmol of the proper benzoyl chloride in 5 mL of toluene was added. The mixture was heated to reflux for 2-24 hr, cooled and washed with water (10 mL), HCl 10% (10 mL) and water (2 x 10mL). The solution was dried over sodium sulfate and concentrated to dryness at reduced pressure to obtaincrude *N*-(2-[*N*'-phenyl-*N*'-acetamidomethyl])benzanilides (**5**) that were purified by crystallization from ethanol.

N-(2-[N'-(4-Bromophenyl)acetamidomethyl])benzanilide (5a). N-(4-Bromophenyl)-N-(2-aminobenzyl)acetamide (4a) (638 mg, 2 mmol) was reacted with benzoyl chloride (281 mg, 2 mmol) to give N-(2-[N'-(4-bromophenyl)acetamidomethyl])benzanilide 5a as a colorless solid (685 mg, 81%), mp = 203-204 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-d): δ 10.71 (s, 1H, NH), 8.20 (dd, J 7.8, 1.8 Hz, 2H, aromatic), 8.13 (d, J 8.1 Hz, 1H, aromatic), 7.58 (d, J 8.5 Hz, 2H, aromatic), 7.56 – 7.51 (m, 3H, aromatic), 7.37 (m, 1H, aromatic), 7.00 - 6.94 (m, 3H, aromatic), 6.71 (d, J 7.6 Hz, 1H, aromatic), 4.80 (s, 2H, CH_2), 1.83 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.33 (C=O), 166.59 (C=O), 141.70, 136.93, 135.01, 133.38, 131.80, 131.39, 130.23, 129.13, 128.62, 128.00, 127.12, 125.32, 124.37, 122.71, 50.43 (CH_2), 22.66 (CH_3). Elem. Anal. $C_{22}H_{19}BrN_2O_2$; found C, 62.46; H, 4.55; N, 6.63%; requires C, 62.42; H, 4.52; Br, 18.88; N, 6.62; O, 7.56%.

***N*-(2-[*N*'-(2-Chlorophenyl)acetamidomethyl])benzanilide (5b).** *N*-(2-Chlorophenyl)-*N*-(2-aminobenzyl)acetamide (**4b**) (549 mg, 2 mmol) was reacted with benzoyl chloride (281 mg, 2 mmol) to give *N*-(2-[*N'*-(2-chlorophenyl)acetamidomethyl])benzanilide **5b** as a colorless solid (545 mg, 72%), mp = 160-161 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.74 (s, 1H, NH), 8.25 – 8.19 (m, 2H, aromatic), 8.16 (dd, *J* 8.3, 1.2 Hz, 1H, aromatic), 7.60 – 7.50 (m, 4H, aromatic), 7.41 – 7.35 (m, 2H, aromatic), 7.32 (td, *J* 7.6, 1.5 Hz, 1H, aromatic), 7.02 (dd, *J* 7.8, 1.6 Hz, 1H, aromatic), 6.97 (td, *J* 7.4, 1.2 Hz, 1H, aromatic), 6.69 (dd, *J* 7.6, 1.6 Hz, 1H, aromatic), 5.23 (d, *J* 14.7 Hz, 1H, C**H**H), 4.31 (d, *J* 14.7 Hz, 1H, CH**H**), 1.82 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.81 (C=O), 166.67 (C=O), 139.69, 137.20, 135.09, 133.11, 131.77, 131.51, 131.27, 131.07, 130.26, 129.06, 128.60, 128.19, 128.05, 126.98, 125.10, 124.24, 49.19 (CH_2), 22.23 (CH_3). Elem. Anal. $C_{22}H_{19}ClN_2O_2$; found C, 69.66; H, 5.08; N, 7.40%; requires C, 69.75; H, 5.06; Cl, 9.36; N, 7.39; O, 8.45%.

***N*-(2-[*N*'-(4-Chlorophenyl)acetamidomethyl])benzanilide (5c).** *N*-(4-Chlorophenyl)-*N*-(2-aminobenzyl)acetamide (**4c**) (549 mg, 2 mmol) was reacted with benzoyl chloride (281 mg, 2 mmol) to give *N*-(2-[*N'*-(4-chlorophenyl)acetamidomethyl])benzanilide **5c** as a colorless solid (590 mg, 78%), mp = 202-203 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.72 (s, 1H, NH), 8.20 (dd, *J* 7.9, 1.5 Hz, 2H, aromatic), 8.13 (d, *J* 8.1 Hz, 1H, aromatic), 7.61 – 7.49 (m, 3H, aromatic), 7.42 (d, *J* 8.6 Hz, 2H, aromatic), 7.39 – 7.33 (m, 1H, aromatic), 7.01 (d, *J* 8.6 Hz, 2H, aromatic), 6.98 (t, *J* 7.6 Hz, 1H, aromatic), 6.71 (dd, *J* 7.6, 1.6 Hz, 1H, aromatic), 4.80 (s, 2H, CH_2), 1.83 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.40 (C=O), 166.59 (C=O), 141.17, 136.94, 135.00, 134.69, 131.80, 131.39, 130.36, 129.90, 129.12, 128.61, 128.00, 127.13, 125.30, 124.35, 50.46 (CH_2), 22.64 (CH_3). Elem. Anal. $C_{22}H_{19}ClN_2O_2$; found C, 69.72; H, 5.01; N, 7.36%; requires C, 69.75; H, 5.06; Cl, 9.36; N, 7.39; O, 8.45%.

***N*-(2-[*N*'-(2-Fluorophenyl)acetamidomethyl])benzanilide (5d).** *N*-(2-Fluorophenyl)-*N*-(2-aminobenzyl)acetamide (**4d**) (516 mg, 2 mmol) was reacted with benzoyl chloride (281 mg, 2 mmol) to give *N*-(2-[*N'*-(2-fluorophenyl)acetamidomethyl])benzanilide **5d** as a colorless solid (550 mg, 76%), mp = 112-113 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.70 (s, 1H, NH), 8.24 – 8.20 (m, 2H, aromatic), 8.14 (dd, *J* 8.3, 1.2 Hz, 1H, aromatic), 7.58 – 7.52 (m, 3H, aromatic), 7.44 – 7.40 (m, 1H, aromatic), 7.36 (ddd, *J* 8.6, 7.6, 1.6 Hz, 1H, aromatic), 7.24 – 7.20 (m, 2H, aromatic), 7.08 (td, *J* 7.7, 1.7 Hz, 1H, aromatic), 6.97 (td, *J* 7.5, 1.3 Hz, 1H, aromatic), 6.71 (dd, *J* 7.7, 1.6 Hz, 1H, aromatic), 5.03 (d, *J* 14.6 Hz, 1H, C**H**H), 4.56 (d, *J* 14.6 Hz, 1H, CH**H**), 1.86 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.95 (C=O), 166.61 (C=O), 158.04 (d, *J* 250.8 Hz, C-F aromatic), 136.98, 135.07, 131.78, 131.15, 130.69 (d, *J* 7.7 Hz), 130.68, 130.66, 129.07, 128.62, 128.02, 127.25, 125.30 (d, *J* 4.1 Hz), 125.18, 124.37, 117.27 (d, *J* 20.0 Hz), 49.76 (CH_2), 22.08 (CH_3). Elem. Anal. $C_{22}H_{19}FN_2O_2$; found C, 73.10; H, 5.22; N, 7.45%; requires C, 72.91; H, 5.28; F, 5.24; N, 7.73; O, 8.83%.

***N*-(2-[*N'*-(4-Fluorophenyl)acetamidomethyl])benzanilide (5e).** *N*-(4-Fluorophenyl)-*N*-(2-aminobenzyl)acetamide (**4e**) (516 mg, 2 mmol) was reacted with benzoyl chloride (281 mg, 2 mmol) to give *N*-(2-[*N'*-(4-fluorophenyl)acetamidomethyl])benzanilide **5e** as a colorless solid (449 mg, 62%), mp = 179-180 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.74 (s, 1H, NH), 8.21 (dd, *J* 7.8, 1.8 Hz, 2H, aromatic), 8.13 (dd, *J* 8.3, 1.2 Hz, 1H, aromatic), 7.60 – 7.49 (m, 3H, aromatic), 7.37 (td, *J* 7.8, 1.6 Hz, 1H, aromatic), 7.13 (m, 2H, aromatic), 7.08 – 7.01 (m, 2H, aromatic), 6.98 (t, *J* 7.4 Hz, 1H, aromatic), 6.71 (dd, *J* 7.7, 1.6 Hz, 1H, aromatic), 4.80 (s, 2H, CH_2), 1.82 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.63 (C=O), 166.62 (C=O), 162.30 (d, *J* 249.3 Hz, C-F aromatic), 138.68 (d, *J* 3.4 Hz), 136.95, 135.01, 131.79, 131.42, 130.30 (d, *J* 8.7 Hz), 129.07, 128.61, 128.01, 127.19, 125.27, 124.31, 117.07 (d, *J* 22.7 Hz), 50.53 (CH_2), 22.62 (CH_3). Elem. Anal. $C_{22}H_{19}FN_2O_2$; found C, 73.09; H, 5.20; N, 7.60%; requires C, 72.91; H, 5.28; F, 5.24; N, 7.73; O, 8.83%.

***N*-(2-[*N'*-(4-Iodophenyl)acetamidomethyl])benzanilide (5f).** *N*-(4-Iodophenyl)-*N*-(2-aminobenzyl)acetamide (**4f**) (732 mg, 2 mmol) was reacted with benzoyl chloride (281 mg, 2 mmol) to give *N*-(2-[*N'*-(4-iodophenyl)acetamidomethyl])benzanilide **5f** as a colorless solid (433 mg, 46%), mp = 178-179 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.72 (s, 1H, NH), 8.23 – 8.17 (m, 2H, aromatic), 8.12 (d, *J* 8.2 Hz, 1H, aromatic), 7.78 (d, *J* 8.4 Hz, 2H, aromatic), 7.57 – 7.50 (m, 3H, aromatic), 7.36 (t, *J* 7.4 Hz, 1H, aromatic), 6.98 (t, *J* 7.5 Hz, 1H, aromatic), 6.82 (d, *J* 8.4 Hz, 2H, aromatic), 6.71 (d, *J* 7.4 Hz, 1H, aromatic), 4.79 (s, 2H, CH_2), 1.83 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.27 (C=O), 166.56 (C=O), 142.38, 139.35, 136.89, 134.98, 131.78, 131.36, 130.43, 129.09, 128.60, 127.98, 127.14, 125.29, 124.36, 94.15, 50.38 (CH_2), 22.64 (CH_3). Elem Anal. $C_{22}H_{19}IN_2O_2$; found C, 56.25; H, 4.10; N, 5.97%; requires C, 56.18; H, 4.07; I, 26.98; N, 5.96; O, 6.80%.

2-Chloro-*N*-(2-[*N'*-(4-bromophenyl)acetamidomethyl])benzanilide (5g). *N*-(4-Bromophenyl)-*N*-(2-aminobenzyl)acetamide (**4a**) (638 mg, 2 mmol) was reacted with 2-chlorobenzoyl chloride (350 mg, 2 mmol) to give 2-chloro-*N*-(2-[*N'*-(4-bromophenyl)acetamidomethyl])benzanilide **5g** as a colorless solid (814 mg, 89%), mp = 154-155 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.27 (s, 1H, NH), 8.34 (d, *J* 8.2 Hz, 1H, aromatic), 7.66 (dd, *J* 6.7, 2.5 Hz, 1H, aromatic), 7.53 (d, *J* 8.5 Hz, 2H, aromatic), 7.48 (dd, *J* 7.2, 2.1 Hz, 1H, aromatic), 7.43 – 7.34 (m, 3H, aromatic), 6.96 (td, *J* 7.5, 1.2 Hz, 1H, aromatic), 6.87 (d, *J* 8.5 Hz, 2H, aromatic), 6.69 (dd, *J* 7.6, 1.6 Hz, 1H, aromatic), 4.81 (s, 2H, CH_2), 1.74 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.37 (C=O), 166.12 (C=O), 141.18, 136.70, 136.66, 133.29, 131.58, 131.28, 131.18, 130.25, 130.12, 129.37, 129.24, 127.01, 126.28, 124.36, 123.62, 122.67, 50.37 (CH_2), 22.49 (CH_3). Elem. Anal. $C_{22}H_{18}ClBrN_2O_2$; found C, 57.80; H, 4.00; N, 6.19%; requires C, 57.73; H, 3.96; Br, 17.46; Cl, 7.74; N, 6.12; O, 6.99%.

2-Chloro-*N*-(2-[*N'*-(2-chlorophenyl)acetamidomethyl])benzanilide (5h). *N*-(2-Chlorophenyl)-*N*-(2-aminobenzyl)acetamide (**4b**) (549 mg, 2 mmol) was reacted with 2-chlorobenzoyl chloride (350 mg, 2 mmol) to give 2-chloro-*N*-(2-[*N'*-(2-chlorophenyl)acetamidomethyl])benzanilide **5h** as a colorless solid (570 mg, 69%), mp = 112-113 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.32 (s, 1H, NH), 8.38 (d, *J* 8.2 Hz, 1H, aromatic), 7.71 – 7.65 (m, 1H, aromatic), 7.52 (dd, *J* 8.0, 1.4 Hz, 1H, aromatic), 7.50 – 7.46 (m, 1H, aromatic), 7.43 – 7.32 (m, 4H, aromatic), 7.29 – 7.24 (m, 1H, aromatic), 6.97 – 6.88 (m, 2H, aromatic), 6.66 (dd, *J* 7.6, 1.6 Hz, 1H, aromatic), 5.26 (d, *J* 14.8 Hz, 1H, C**H**H), 4.32 (d, *J* 14.8 Hz, 1H, CH**H**), 1.72 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.88 (C=O), 166.20 (C=O), 139.17, 137.05, 136.73, 133.09, 131.64, 131.40, 131.16, 131.13, 130.98, 130.28, 130.23, 129.35, 129.28, 128.17, 126.98, 126.15, 124.23, 123.43, 49.13 (CH_2), 22.04 (CH_3). Elem. Anal. $C_{22}H_{18}Cl_2N_2O_2$; found C, 63.80; H, 4.48; N, 6.77%; requires C, 63.93; H, 4.39; Cl, 17.15; N, 6.78; O, 7.74%.

2-Chloro-*N*-(2-[*N'*-(4-chlorophenyl)acetamidomethyl])benzanilide (5i). *N*-(4-Chlorophenyl)-*N*-(2-aminobenzyl)acetamide (**4c**) (549 mg, 2 mmol) was reacted with 2-chlorobenzoyl chloride (350 mg, 2 mmol) to give 2-chloro-*N*-(2-[*N'*-(4-chlorophenyl)acetamidomethyl])benzanilide **5i** as a colorless solid (446 mg, 54%), mp

= 162-163 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.27 (s, 1H, NH), 8.35 (d, *J* 7.8 Hz, 1H, aromatic), 7.67 (s broad, 1H, aromatic), 7.48 (d, *J* 7.1 Hz, 1H, aromatic), 7.45 – 7.32 (m, 5H, aromatic), 7.01 – 6.90 (m, 3H, aromatic), 6.69 (d, *J* 7.3 Hz, 1H, aromatic), 4.82 (s, 2H, CH_2), 1.74 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.50 (C=O), 166.18 (C=O), 140.66, 136.72, 136.68, 134.68, 131.62, 131.31, 131.21, 130.31, 130.28, 129.87, 129.40, 129.36, 127.07, 126.32, 124.38, 123.68, 50.57 (CH_2), 22.61 (CH_3). Elem. Anal. $C_{22}H_{18}Cl_2N_2O_2$; found C, 63.85; H, 4.45; N, 6.83%; requires C, 63.93; H, 4.39; Cl, 17.15; N, 6.78; O, 7.74%.

2-Chloro-*N*-(2-[*N'*-(2-fluorophenyl)acetamidomethyl])benzanilide (5j). *N*-(2-Fluorophenyl)-*N*-(2-aminobenzyl)acetamide (**4d**) (516 mg, 2 mmol) was reacted with 2-chlorobenzoyl chloride (350 mg, 2 mmol) to give 2-chloro-*N*-(2-[*N'*-(2-fluorophenyl)acetamidomethyl])benzanilide **5j** as a colorless solid (594 mg, 75%), mp = 62-63 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.25 (s, 1H, NH), 8.34 (d, *J* 8.2 Hz, 1H, aromatic), 7.70 – 7.66 (m, 1H, aromatic), 7.50 – 7.46 (m, 1H, aromatic), 7.43 – 7.33 (m, 4H, aromatic), 7.20 – 7.13 (m, 2H, aromatic), 6.98 (td, *J* 7.5, 1.7 Hz, 1H, aromatic), 6.94 (td, *J* 7.5, 1.2 Hz, 1H, aromatic), 6.68 (dd, *J* 7.5, 1.6 Hz, 1H, aromatic), 5.07 (d, *J* 14.7 Hz, 1H, C**H**H), 4.55 (d, *J* 14.7 Hz, 1H, CH**H**), 1.76 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 172.00 (C=O), 166.16 (C=O), 158.02 (d, *J* 250.7 Hz, C-F aromatic), 136.79, 136.70, 131.35, 131.32, 131.16, 130.66 (*J* 7.9 Hz), 130.59, 130.28, 129.63 (d, *J* 12.9 Hz), 129.32, 129.27, 126.98, 126.43, 125.23 (d, *J* 4.0 Hz), 124.33, 123.56, 117.16 (d, *J* 20.0 Hz), 49.64 (CH_2), 21.90 (CH_3). Elem. Anal. $C_{22}H_{18}ClFN_2O_2$; found C, 66.51; H, 4.55; N, 7.02%; requires C, 66.59; H, 4.57; Cl, 8.93; F, 4.79; N, 7.06; O, 8.06%.

2-Chloro-*N*-(2-[*N'*-(4-fluorophenyl)acetamidomethyl])benzanilide (5k). *N*-(4-Fluorophenyl)-*N*-(2-aminobenzyl)acetamide (**4e**) (516 mg, 2 mmol) was reacted with 2-chlorobenzoyl chloride (350 mg, 2 mmol) to give 2-chloro-*N*-(2-[*N'*-(4-fluorophenyl)acetamidomethyl])benzanilide **5k** as a colorless solid (515 mg, 65%), mp = 135-136 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.30 (s, 1H, NH), 8.35 (d, *J* 8.2 Hz, 1H, aromatic), 7.69 – 7.65 (m, 1H, aromatic), 7.48 (dd, *J* 7.0, 2.1 Hz, 1H, aromatic), 7.44 – 7.34 (m, 3H, aromatic), 7.08 (t, *J* 8.5 Hz, 2H, aromatic), 6.99 – 6.93 (m, 3H, aromatic), 6.68 (dd, *J* 7.6, 1.6 Hz, 1H, aromatic), 4.81 (s, 2H, CH_2), 1.73 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.69 (C=O), 166.16 (C=O), 162.26 (d, *J* 249.3 Hz, C-F aromatic), 138.15 (d, *J* 3.4 Hz), 136.73, 136.68, 131.62, 131. 29, 131.17, 130.25, 130.20 (d, *J* 8.8 Hz), 129.34, 129.23, 127.00, 126.36, 124.30, 123.59, 116.99 (*J* 22.8 Hz), 50.50 (CH_2), 22.45 (CH_3). Elem. Anal. $C_{22}H_{18}ClFN_2O_2$; found C, 66.50; H, 4.51; N, 7.09%; requires C, 66.59; H, 4.57; Cl, 8.93; F, 4.79; N, 7.06; O, 8.06%.

2-Chloro-*N*-(2-[*N'*-(4-iodophenyl)acetamidomethyl])benzanilide (5l). *N*-(4-Iodophenyl)-*N*-(2-aminobenzyl)acetamide (**4f**) (732 mg, 2 mmol) was reacted with 2-chlorobenzoyl chloride (350 mg, 2 mmol) to give 2-chloro-*N*-(2-[*N'*-(4-iodophenyl)acetamidomethyl])benzanilide **5l** as a colorless solid (685 mg, 68%), mp = 143-144 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.27 (s, 1H, NH), 8.34 (d, *J* 8.2 Hz, 1H, aromatic), 7.73 (d, *J* 8.4 Hz, 2H, aromatic), 7.66 (dd, *J* 6.9, 2.0 Hz, 1H, aromatic), 7.47 (d, *J* 7.2 Hz, 1H, aromatic), 7.39 (m, 3H, aromatic), 6.97 (t, *J* 7.5 Hz, 1H, aromatic), 6.74 (d, *J* 8.3 Hz, 2H, aromatic), 6.69 (d, *J* 7.4 Hz, 1H, aromatic), 4.81 (s, 2H, CH_2), 1.74 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.33 (C=O), 166.12 (C=O), 141.91, 139.29, 136.70, 136.67, 131.58, 131.29, 131.18, 130.34, 130.26, 129.37, 129.24, 127.01, 126.32, 124.37, 123.65, 94.17, 50.35 (CH_2), 22.51 (CH_3). Elem. Anal. $C_{22}H_{18}ClIN_2O_2$; found C, 52.24; H, 3.66; N, 5.60%; requires C, 52.35; H, 3.59; Cl, 7.02; I, 25.14; N, 5.55; O, 6.34%.

2-Nitro-*N*-(2-[*N'*-(4-bromophenyl)acetamidomethyl])benzanilide (5m). *N*-(4-Bromophenyl)-*N*-(2-aminobenzyl)acetamide (**4a**) (638 mg, 2 mmol) was reacted with 2-nitrobenzoyl chloride (371 mg, 2 mmol) to give 2-nitro-*N*-(2-[*N'*-(4-bromophenyl)acetamidomethyl])benzanilide **5m** as a pale yellow solid (309 mg, 33%), mp = 185-186 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.43 (s, 1H, NH), 8.41 (dd, *J* 8.2, 1.1 Hz, 1H, aromatic), 8.17 (d, *J* 8.2 Hz, 1H, aromatic), 7.81 – 7.72 (m, 2H, aromatic), 7.63 (ddd, *J* 8.6, 6.4, 2.4 Hz, 1H, aromatic), 7.42 – 7.32 (m, 3H, aromatic), 6.97 – 6.89 (m, 3H, aromatic), 6.64 (dd, *J* 7.6, 1.5 Hz, 1H, aromatic), 4.77 (s, 2H, CH_2), 1.70 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.93 (C=O), 165.39 (C=O), 146.32, 140.28, 136.84, 134.73, 134.04, 133.62, 131.73, 130.57, 130.30, 129.74, 129.63, 129.23, 125.66, 124.63, 124.27, 123.01, 50.51 (CH_2), 22.31 (CH_3). Elem. Anal. $C_{22}H_{18}BrN_3O_4$; found C, 56.44; H, 3.87; N, 8.99%; requires C, 56.42; H, 3.87; Br, 17.06; N, 8.97; O, 13.67%.

2-Nitro-*N*-(2-[*N'*-(2-chlorophenyl)acetamidomethyl])benzanilide (5n). *N*-(2-Chlorophenyl)-*N*-(2-aminobenzyl)acetamide (**4b**) (549 mg, 2 mmol) was reacted with 2-nitrobenzoyl chloride (371 mg, 2 mmol) to give 2-nitro-*N*-(2-[*N'*-(2-chlorophenyl)acetamidomethyl])benzanilide **5n** as a pale yellow solid (508 mg, 60%), mp = 114-115 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.49 (s, 1H, NH), 8.43 (d, *J* 8.2 Hz, 1H, aromatic), 8.17 (d, *J* 8.2 Hz, 1H, aromatic), 7.78 (d, *J* 4.4 Hz, 2H, aromatic), 7.64 (dt, *J* 8.5, 4.4 Hz, 1H, aromatic), 7.52 (dd, *J* 8.0, 1.4 Hz, 1H, aromatic), 7.41 – 7.33 (m, 2H, aromatic), 7.28 – 7.23 (m, 1H, aromatic), 6.93 (t, *J* 7.4 Hz, 1H, aromatic), 6.88 (dd, *J* 7.8, 1.6 Hz, 1H, aromatic), 6.61 (dd, *J* 7.6, 1.5 Hz, 1H, aromatic), 5.23 (d, *J* 14.8 Hz, 1H, C**H**H), 4.26 (d, *J* 14.8 Hz, 1H, CH**H**), 1.68 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 172.37 (C=O), 165.41 (C=O), 146.46, 138.78, 137.16, 134.01, 133.66, 132.90, 131.75, 131.19, 130.93, 130.56, 130.31, 129.61, 129.28, 128.23, 125.58, 124.64, 124.17, 122.86, 49.17 (CH_2), 21.87 (CH_3). Elem. Anal. $C_{22}H_{18}ClN_3O_4$; found C, 62.28; H, 4.25; N, 9.99%; requires C, 62.34; H, 4.28; Cl, 8.36; N, 9.91; O, 15.10%.

2-Nitro-*N*-(2-[*N'*-(4-chlorophenyl)acetamidomethyl])benzanilide (5o). *N*-(4-Chlorophenyl)-*N*-(2-aminobenzyl)acetamide (**4c**) (549 mg, 2 mmol) was reacted with 2-nitrobenzoyl chloride (371 mg, 2 mmol) to give 2-nitro-*N*-(2-[*N'*-(4-chlorophenyl)acetamidomethyl])benzanilide **5o** as a pale yellow solid (263 mg, 31%), mp = 174-175 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.42 (s, 1H, NH), 8.40 (d, *J* 8.1 Hz, 1H, aromatic), 8.17 (d, *J* 8.2 Hz, 1H, aromatic), 7.81 – 7.72 (m, 2H, aromatic), 7.63 (ddd, *J* 8.6, 6.5, 2.2 Hz, 1H, aromatic), 7.52 (d, *J* 8.5 Hz, 2H, aromatic), 7.41 – 7.34 (m, 1H, aromatic), 6.95 (td, *J* 7.5, 1.2 Hz, 1H, aromatic), 6.86 (d, *J* 8.5 Hz, 2H, aromatic), 6.64 (dd, *J* 7.6, 1.5 Hz, 1H, aromatic), 4.77 (s, 2H, CH_2), 1.70 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.86 (C=O), 165.39 (C=O), 146.32, 140.81, 136.84, 134.05, 133.63, 133.32, 131.74, 130.57, 130.13, 130.07, 129.65, 129.24, 125.64, 124.65, 124.29, 123.02, 50.49 (CH_2), 22.34 (CH_3). Elem. Anal. $C_{22}H_{18}ClN_3O_4$; found C, 62.30; H, 4.20; N, 9.84%; requires C, 62.34; H, 4.28; Cl, 8.36; N, 9.91; O, 15.10%.

2-Nitro-*N*-(2-[*N'*-(2-fluorophenyl)acetamidomethyl])benzanilide (5p). *N*-(2-Fluorophenyl)-*N*-(2-aminobenzyl)acetamide (**4d**) (516 mg, 2 mmol) was reacted with 2-nitrobenzoyl chloride (371 mg, 2 mmol) to give 2-nitro-*N*-(2-[*N'*-(2-fluorophenyl)acetamidomethyl])benzanilide **5p** as a pale yellow solid (326 mg, 40%), mp = 160-161 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.43 (s, 1H, NH), 8.39 (dd, *J* 8.2, 1.2 Hz, 1H, aromatic), 8.17 (d, *J* 8.2 Hz, 1H, aromatic), 7.78 – 7.77 (m, 2H, aromatic), 7.64 (ddd, *J* 8.1, 3.8, 3.7 Hz, 1H, aromatic), 7.36 – 7.40 (m, 2H, aromatic), 7.20 – 7.13 (m, 2H, aromatic), 6.94 (tdd, *J* 7.4, 5.4, 1.5 Hz, 2H, aromatic), 6.64 (dd, *J* 7.6, 1.6 Hz, 1H, aromatic), 5.10 (d, *J* 14.8 Hz, 1H, C**H**H), 4.44 (d, *J* 14.8 Hz, 1H, CH**H**), 1.73 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 172.48 (C=O), 165.38 (C=O), 157.93 (d, *J* 250.7 Hz, C-F aromatic), 146.45, 136.91, 134.00, 133.66, 131.48, 130.77, 130.76 (d, *J* 7.7 Hz), 130.57, 129.60, 129.33, 129.26, 125.90, 125.28 (d, *J* 4.0 Hz), 124.67, 124.29, 123.07, 117.13 (d, *J* 19.9 Hz), 49.66 (CH_2), 21.79 (CH_3). Elem. Anal. $C_{22}H_{18}FN_3O_4$; found C, 64.87; H, 4.48; N, 10.39%; requires C, 64.86; H, 4.45; F, 4.66; N, 10.31; O, 15.71%.

2-Nitro-*N*-(2-[*N'*-(4-fluorophenyl)acetamidomethyl])benzanilide (5q). *N*-(4-Fluorophenyl)-*N*-(2-aminobenzyl)acetamide (**4e**) (516 mg, 2 mmol) was reacted with 2-nitrobenzoyl chloride (371 mg, 2 mmol) to give 2-nitro-*N*-(2-[*N'*-(4-fluorophenyl)acetamidomethyl])benzanilide **5q** as a pale yellow solid (562 mg, 69%), mp = 173-174 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.45 (s, 1H, NH), 8.41 (d, *J* 8.2 Hz, 1H, aromatic), 8.17 (d, *J* 8.2 Hz, 1H, aromatic), 7.80 – 7.72 (m, 2H, aromatic), 7.63 (ddd, *J* 8.7, 6.3, 2.6 Hz, 1H, aromatic), 7.38 (td, *J* 7.8, 1.6 Hz, 1H, aromatic), 7.07 (m, 2H, aromatic), 6.98 – 6.91 (m, 3H, aromatic), 6.63 (dd, *J* 7.6, 1.5 Hz, 1H, aromatic), 4.77 (s, 2H, CH_2), 1.69 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 172.18 (C=O), 165.42 (C=O), 162.31 (d, *J* 249.3 Hz, C-F aromatic), 146.32, 137.77 (d, *J* 3.3 Hz), 136.86, 134.05, 133.64, 131.76, 130.57, 130.16 (d, *J* 8.7 Hz), 129.61, 129.24, 125.74, 124.64, 124.23, 122.99, 117.02 (d, *J* 22.7 Hz), 50.62 (CH_2), 22.29 (CH_3). Elem. Anal. $C_{22}H_{18}FN_3O_4$; found C, 64.77; H, 4.50; N, 10.46%; requires C, 64.86; H, 4.45; F, 4.66; N, 10.31; O, 15.71%.

2-Nitro-*N*-(2-[*N'*-(4-iodophenyl)acetamidomethyl])benzanilide (5r). *N*-(4-Iodophenyl)-*N*-(2-aminobenzyl)acetamide (**4f**) (732 mg, 2 mmol) was reacted with 2-nitrobenzoyl chloride (371 mg, 2 mmol) to give 2-nitro-*N*-(2-[*N'*-(4-iodophenyl)acetamidomethyl])benzanilide **5r** as a pale yellow solid (330 mg, 32%), mp = 183-184 °C. Spectral Data: ^{1}H NMR (500 MHz, Chloroform-*d*): δ 10.43 (s, 1H, NH), 8.40 (d, *J* 8.2 Hz, 1H, aromatic), 8.17 (d, *J* 8.2 Hz, 1H, aromatic), 7.80 – 7.72 (m, 2H, aromatic), 7.72 (d, *J* 8.4 Hz, 2H, aromatic), 7.63 (ddd, *J* 8.6, 6.7, 2.4 Hz, 1H, aromatic), 7.38 (td, *J* 7.6, 1.5 Hz, 1H, aromatic), 6.95 (t, *J* 7.4 Hz, 1H, aromatic), 6.73 (d, *J* 8.4 Hz, 2H, aromatic), 6.65 (d, *J* 6.8 Hz, 1H, aromatic), 4.76 (s, 2H, CH_2), 1.69 (s, 3H, CH_3). ^{13}C NMR (126 MHz, Chloroform-*d*): δ 171.80 (C=O), 165.38 (C=O), 141.52, 139.31, 136.83, 134.04, 133.63, 131.74, 130.56, 130.29, 129.63, 129.23, 128.33, 125.68, 124.64, 124.30, 123.04, 94.28, 50.45 (CH_2), 22.34 (CH_3). Elem. Anal. $C_{22}H_{18}IN_3O_4$; found C, 51.36; H, 3.55; N, 8.23%; requires C, 51.28; H, 3.52; I, 24.63; N, 8.15; O, 12.42%.

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Supplementary Material

Yields and melting points of compounds **2**, **3** and **4** as well as ^{1}H and ^{13}C spectra are presented in the Supplementary Material associated with this manuscript.

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