Chloroformamidinium Salts: Efficient Reagents for Preparation of 2-Aminobenzoimidazole, 2-Aminobenzoxazole, and 2-Aminobenzothiazole Derivatives

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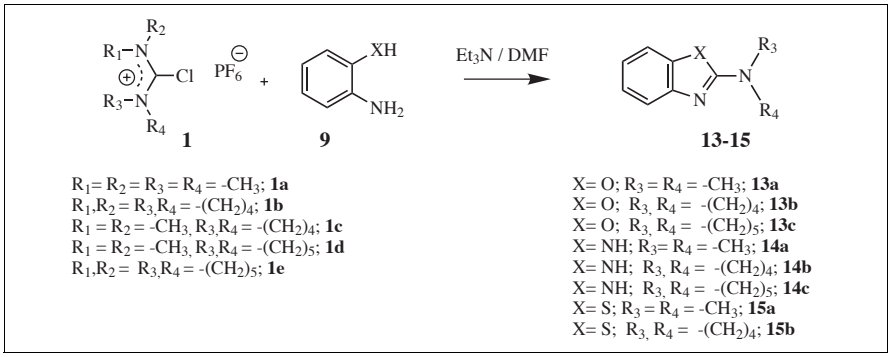
Received July 26, 2005



A Reaction involving chloroformamidinium salts (TCFH **1a**, BTCFH **1b**, DmCFH **1c**, DmPCFH **1d**, BPCFH **1e**) and 2-aminophenol **9a**, benzene-1,2-diamine **9b**, and 2-aminothiophenol **9c** afforded 2-aminobenzoxazole **13**, 2-aminobenzoimidazole **14**, and 2-aminobenzothiazole **15** derivatives, respectively as major products, due to the *in situ* heterocyclization with dimethylamine acting as the better leaving group. Attempts for preparation of **13-15** from the reaction of *N,N*-dimethyl carbomyl chloride **16** with 2-aminophenol **9a**, benzene-1,2-diamine **9b**, and 2-aminothiophenol **9c** were unsuccessful, and gave the unexpected products benzoxazol-2-ol **18a**, benzoimidazol-2-one **18b**, and *S*-(2-amino-phenyl) *N,N*-dimethylthiocarbamate **19** respectively. On the other hand reaction of chloroformamidinium salts **1a-e** with 3-benzyl-2-hydrazinoquinoxaline **3** and 1-hydrazinophthalazine hydrochloride **4** in the presence of triethylamine as a base, afforded the [1,2,4]triazolo derivatives **6** and **7** respectively in good yield and purity. These triazole derivatives were formed due to the strong tendency towards heterocyclization and substitution of dimethylamine group as a better leaving group.

J. Heterocyclic Chem., **43**, 599 (2006).

2-Aminobenzothiazoles are broadly found in bio-organic and medicinal chemistry with application in drug discovery and development for the treatment of diabetes [1], epilepsy [2], inflammation [3], amyotrophic lateral sclerosis [4], analgesia [5], tuberculosis [6], and viral infection [7]. Investigations into the preparation of 2-aminobenzothiazoles can be traced to the early 1900s with the work of Hugeschoff, who found that an arylthiourea can be cyclized by treatment with bromine in chloroform to form a 2-aminobenzothiazole [8]. Several drawbacks are associated with the use of bromine, which is a highly toxic and corrosive reagent, and can be difficult to manipulate on small scale. Recently [9] an organic ammonium tribromides have been used as alternative reagents to bromine.

In recent work [10] we reported the reaction of chloroformamidinium salts **1a** and **1b** with aryl hydrazine derivatives to give 4-amino-1,1,3,3-tetrasubstituted guanidines **2** (Figure 1), as well as reaction with heterocyclic hydrazino derivatives such as 3-benzyl-2-hydazinoquinoxaline **3**, 1-hydrazinophthalazine hydrochloride **4**, and 6-benzyl-5-hydrazino-2*H*-[1,2,4]triazin-3-one **5** to give [1,2,4]triazolo derivatives **6-8** respectively in high yields and purity, due to *in situ* heterocyclization and substitution of one of the dialkylamino groups (Scheme I) [11].

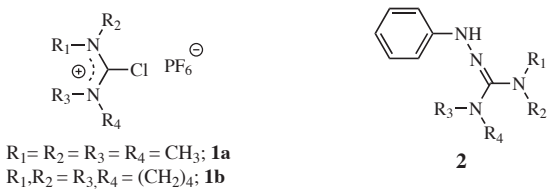
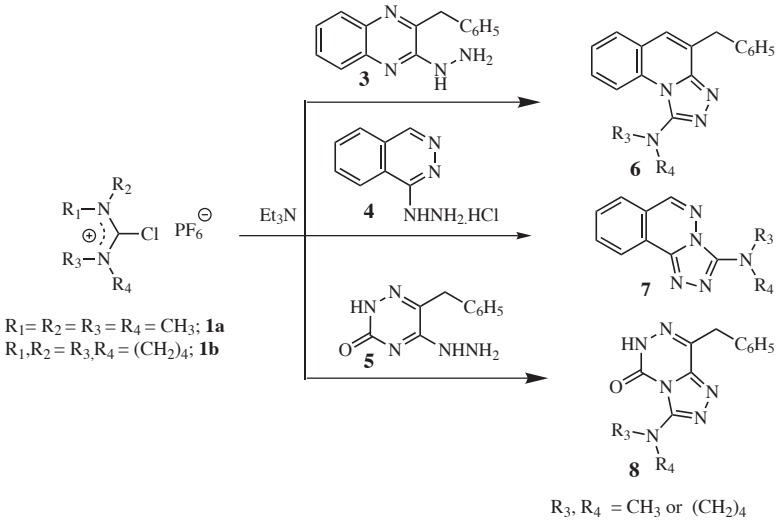


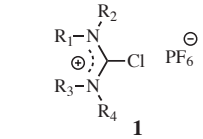
Figure 1

The present work reports a novel and an efficient procedure for preparation of 2-aminobenzoxazole **13**, 2-aminobenzoimidazole **14**, and 2-aminobenzothiazole **15**

derivatives as well as fused [1,2,4]triazolo derivatives **6-8**, which involve the use of chloroformamidinium salts (TCFH, **1a**), (BTCFH, **1b**), (DmTCFH, **1c**), (DmPCFH, **1d**), and (BPCFH, **1e**) (Figure 2).

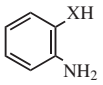
Scheme I





1

$R_1 = R_2 = R_3 = R_4 = -CH_3$; **1a**
$R_1,R_2 = R_3,R_4 = -(CH_2)_4$; **1b**
$R_1 = R_2 = -CH_3$, $R_3,R_4 = -(CH_2)_4$; **1c**
$R_1 = R_2 = -CH_3$, $R_3,R_4 = -(CH_2)_5$; **1d**
$R_1,R_2 = R_3,R_4 = -(CH_2)_5$; **1e**



9

X = O, **9a;** NH, **9b**, or S, **9c**

Figure 2

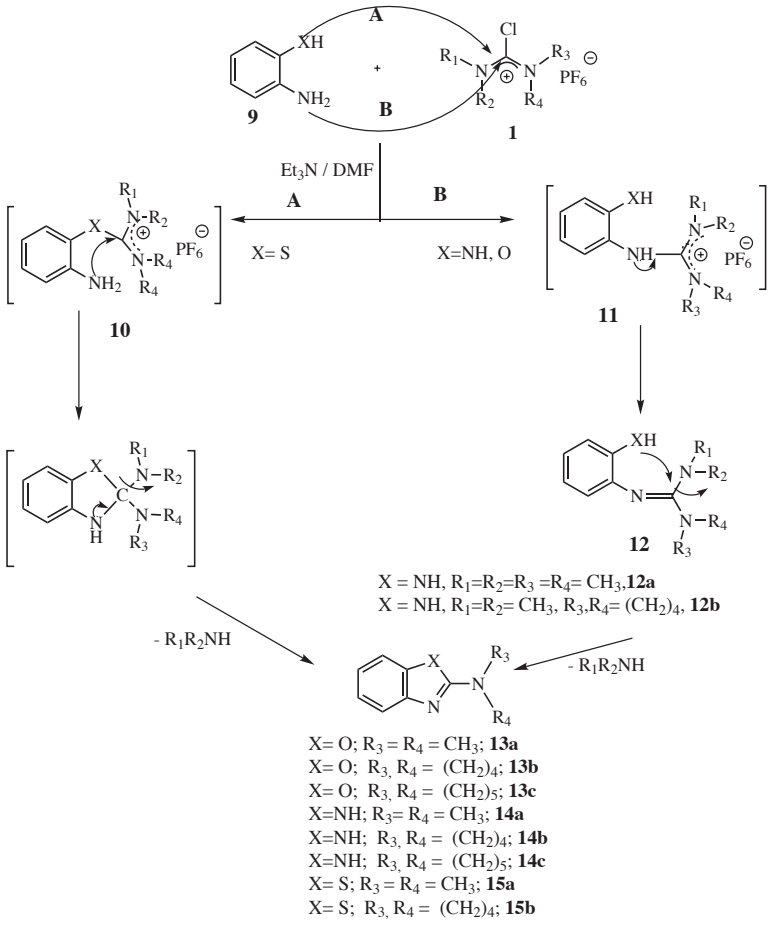
Results and Discussion.

Chloroformamidinium salts **1a-e** were prepared as described previously described [12] and allowed to react with *o*-substituted aniline derivatives **9** to afford the 2-aminobenzoxazole, 2-aminobenzothiazole and 2-amino-benzimidazole derivatives **13-15**. Compounds **13-15** could be formed by two alternative routes (A or B), depending on the nucleophicity of the X substituent of **9**. *Route A*, if X is more nucleophilic than the anilino nitrogen atom, the lone pair of X would first attack the central carbon atom of the chloroformamidinium salts **1** displacing the chloride ion to form intermediate **10** which then under-goes the *in situ* heterocyclization with the loss of dimethylamine as a better leaving group to afford the expected product **15**, as in the case of the reaction of *o*-aminothiophenol **9c** with the chloroformamidinium salts **1**. Otherwise, *route B*, the lone pair of the anilino nitrogen atom will first attack the central carbon atom of the chloroformamidinium salts **1**, to afford intermediate **11** from which a penta-substituted guanidine intermediate **12** is formed which then undergoes *in situ* intramolecular cyclization [11] to afford the azole derivatives **13** and **14**, as in case of the reaction of 2-aminophenol **9a** and benzene-1,2-diamine **9b** with the chloroformamidinium salts **1** (Scheme II).

On the other hand, reaction of chloroformamidinium salts **1a** and **1b** with benzene 1,2-diamine **9b** in dichloromethane (DCM) or dimethylformamide (DMF) as a solvent at room temperature affords a mixture of gaunidine derivatives **12** as major products, while the benzoimidazole derivatives **14** were minor. This was not the case in the reaction with *o*-aminophenol **9a** and *o*-aminothiophenol **9c**.

Attempts to prepare of the azole derivatives **13-15** from the reaction of *N,N*-dimethyl carbamoyl chloride **16** under the same conditions used above were not successful. Reaction of **16** with *o*-aminophenol **9a** and benzene-1,2-diamine **9b** afforded benzoxazol-2-ol **18a** and 1,3-dihydrobenzoimidazol-2-one **18b** as a major product and 2-(*N,N*-dimethyl)aminobenzoxazole **13a** and 2-(*N,N*-dimethyl) aminobenzoimidazole **14a** as a minor product in 2% yield, respectively (Scheme III). This is due to the lone pair of the anilino nitrogen atom firstly attacked the carbonyl carbon atom of **16** forming the intermediate **17** and then undergoing *in situ* intramolecular cyclization with loss of the dimethylamine as a better leaving group to afford **18a** and **18b** as observed from their spectral data. On the other hand, reaction of *N,N*-dimethyl carbamoyl chloride **16** with *o*-aminothiophenol **9c** gave *S*-(2-aminophenyl)-*N,N*-dimethyl thiocarbamate **19**, due to the lone pair of the sulfur atom firstly attacking the

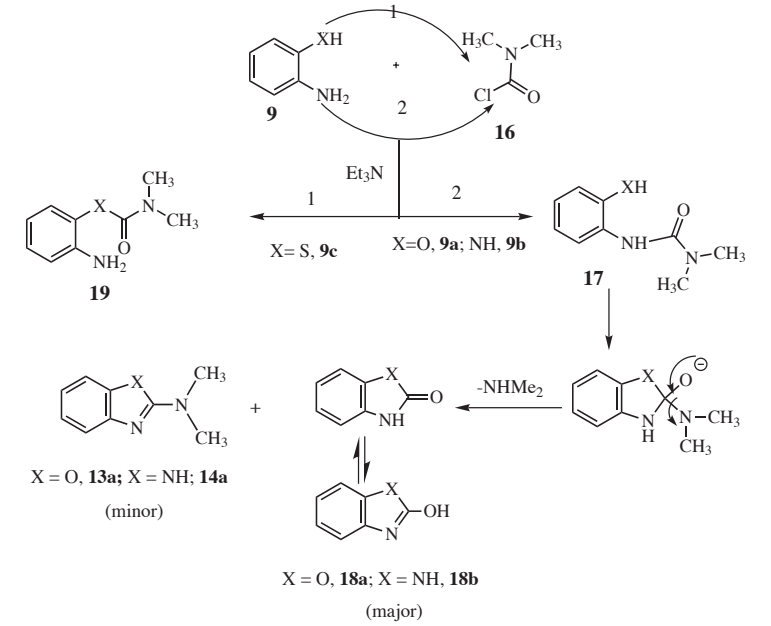
Scheme II



X = NH, R_1=R_2=R_3 =R_4= CH_3,**12a**
X = NH, R_1=R_2= CH_3, R_3,R_4= $(CH_2)_4$, **12b**

X= O; R_3 = R_4 = CH_3; **13a**
X= O; R_3, R_4 = $(CH_2)_4$; **13b**
X= O; R_3, R_4 = $(CH_2)_5$; **13c**
X=NH; R_3= R_4 = CH_3; **14a**
X=NH; R_3, R_4 = $(CH_2)_4$; **14b**
X=NH; R_3, R_4 = $(CH_2)_5$; **14c**
X= S; R_3 = R_4 = CH_3; **15a**
X= S; R_3, R_4 = $(CH_2)_4$; **15b**

Scheme III



X = O, **13a;** X = NH; **14a**
(minor)

X = O, **18a**; X = NH, **18b**
(major)

carbonyl carbon atom of **16** forming **19** as a major product based on its spectral data (Scheme III).

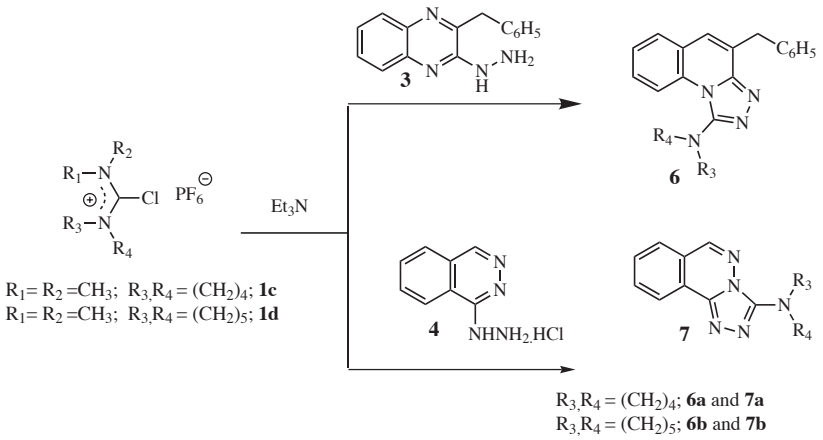
The ir spectrum of **18a** showed two absorption peaks at 3500 and 1640 cm^{-1} corresponding to the hydroxyl and the imine groups, respectively. The ^1H NMR spectrum of **18a** showed a doublet of doublet (δ=7.26, J_{ortho}=7.2 Hz, J_{meta}=1.5 Hz) corresponding to the aromatic hydrogen in the *ortho* position with respect to the oxygen atom. A multiplet corresponding to the three aromatic hydrogen atoms was also observed in the region δ 7.16-7.03. The hydrogen of the hydroxyl group was observed by a broad singlet at δ 3.48. The ^{13}C NMR spectrum of **18a** showed the expected signals. The imine carbon was observed at δ 155.05, while six signals corresponding to the six aromatic carbons were located in the region δ 143.53-109.80. Mass spectral analysis of **18a** showed an ion peak at 135 amu corresponding to the molecular weight of **18a**.

The ir spectrum of compound **18b** showed one NH absorption at 3170 cm^{-1} and strong absorption for the carbonyl group at 1760 cm^{-1}. Also the ^1H NMR spectrum was consistent with the suggested structure. A singlet due to the hydrogen of the two NH groups was observed at δ 10.57. Another singlet assigned to the four aromatic hydrogen atoms was observed at δ 6.91. The ^{13}C NMR spectrum of **18b** showed four resolved carbon signals. The low-field carbon signal at δ 154.12 was assigned to the carbonyl carbon. Three signals were observed in the aromatic region at δ 128.02, 119.37 and 107.44 assigned each to the two quaternary, two *ortho* and *meta* carbon atoms of the aromatic ring, respectively. Mass spectral analysis of **18b** gave an ion peak at 134.05 amu, corresponding to the molecular weight of **18b** which is consistent with the assigned structure.

The ir spectrum of **19** showed two absorption peaks at 3440 and 3340 cm^{-1} due to the -NH_2 group, and an absorption peak at 1660 cm^{-1} expected for the C=O group. The ^1H NMR spectrum showed a multiplet (δ=7.13-7.09), a doublet of doublets (δ=6.72, J_{ortho}=8.4 Hz, J_{meta}=1.3 Hz), and a triplet of doublets (δ=7.50, J_{ortho}=7.4 Hz, J_{meta}=1.3 Hz) corresponding to the four aromatic hydrogen atoms. A singlet at δ 5.26 corresponding to the two hydrogen atoms of the -NH_2 group was observed. The two methyl groups were observed as two 3-proton singlets (δ=3.05 and 2.90). The ^{13}C NMR spectrum of **19** showed eight resolved carbon signals. The carbonyl carbon signal was observed at δ 165.65, while six signals corresponding to six aromatic carbon atoms were located in the region δ 150.79-110.35. A signal for the two methyl groups was observed at δ 36.89. Mass spectral analysis of **19** gave an ion peak at 196.15 amu corresponding to the molecular weight of **19**.

Chloroformamidinium salts (DmTCFH, **1c**) and (DmPCFH, **1d**) also, reacted with 3-benzyl-2-hydrazino-quinoxaline **3** and 1-hydrazinophthalazine hydrochloride **4** in the presence of triethyl amine as a base, to afford the [1,2,4]triazolo derivatives **6** and **7**, respectively in good yield and purity (Scheme IV). These triazole derivatives have been prepared previously [10], and formed due to the strong tendency towards heterocyclization [11] and substitution of the diemthylamine group which acted as the better leaving group verified by their spectroscopic data, mass spectra, and elemental analysis.

Scheme IV



Conclusions.

We have successfully demonstrated the versatility of chloroformamidinium salts **1a-e** as useful reagents for the

synthesis of 2-aminobenzoxazole **13**, 2-aminobenzimidazole **14**, and 2-aminobenzothiazole **15** derivatives as well as [1,2,4]triazolo derivatives **6** and **7**.

EXPERIMENTAL

General.

Abbreviation used in the text: TCFH = 1,1,3,3-tetramethylchloroformamidinium hexafluorophosphate; BTCFH = *bis*-(tetramethylene)chloroformamodinium hexafluorophosphate; BPCFH = *bis*-(pentaramethylene) chloroformamodinium hexafluorophosphate DmTCFH = 1,1-dimethyl- 3,3-tetramethylene chloroformamidinium hexafluorophosphate; DmPCFH = 1,1-dimethyl-3,3-pentamethylene chloroformamidinium hexafluorophosphate; DMF = dimethylformamide; DCM = dichloromethane; Et_3N = triethylamine.

Column chromatography was performed using silica gel 60 obtained from Fluka Chemie (CH-9470, Mesh <230 ASTM). TLC was performed using silica 8×4 cm plates from Albet using suitable solvent systems with spots being visualized by a Spectroline UV Lamp Model CM-10 (254 nm). All solvents used for recrystallization, extraction, column chromatography and TLC were commercial grade, and distilled before use. Melting points were obtained in open capillary tubes using Gallenkamp Sanyo melting point apparatus and were uncorrected. Infrared spectra (IR) were recorded in KBr pellets on a Shimadzu 8300 series Fourier Transformer Instrument. Ultraviolet (UV) spectra were taken with a Helios α-Spectronic Unicam spectrophotometer using a quartz sample cell of 1 cm path length. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at ambient temperature. Tetramethylsilane (TMS) was used as reference for all NMR spectra with chemical shifts reported as ppm relative to TMS. Mass spectra (MS) [m/z (% rel. int.)] were recorded on Shimadzu GC-MS QP 5050 A spectrometer using electron impact (EI) at 70 eV. Elemental analyses were carried out at the University of Cairo Microanalytical Laboratories.

General Procedure for Preparation of Urea Derivatives [12].

N,N-Dimethyl carbamoyl chloride **16** (55.05 ml, 0.6 moles) was added dropwise to a stirred mixture of a secondary amine (0.5 moles) and triethylamine (69.6 ml, 0.5 moles) in dry methylene chloride (400 ml) at 0 ºC. When the addition was completed, the mixture was stirred overnight at room temperature. The reaction mixture was then washed with water (100 ml), 10% HCl (100 ml), saturated sodium carbonate solution (100 ml), water (100 ml), and then saturated sodium chloride (100 ml), dried over anhydrous Na_2SO_4, filtered, and then the solvent removed under reduced pressure. The oily residue product was purified by simple or vacuum distillation.

1,1-Dimethyl-3,3-tetramethylene Urea (DmTU) [12c].

The product obtained as yellow oil in yield of 77.5%, b.p. 144 -147 ºC. ^{1}H nmr ($CDCl_3$): δ 1.80-2.10 (m, 4 H, 2 CH_2), 2.72 (s, 6 H, 2 CH_3), 3.27-3.49 (m, 4 H, 2 CH_2) ppm.

1,1-Dimethyl-3,3-pentamethylene Urea (DmPU) [12c].

The product obtained as yellow oil in yield of 77.5%, b.p. 147-151 ºC. ^{1}H nmr ($CDCl_3$): δ 1.47-1.48 (m, 6 H, 3 CH_2), 2.72 (s, 6 H, 2 CH_3), 3.07-3.09 (m, 4 H, 2 CH_2) ppm.

General Procedure for Preparation of Chloroformamidinium salts (**1**) [12].

Oxalyl chloride (8.59 ml, 100 mmoles) was added dropwise to a solution of urea derivative (100 mmoles) in dry CH_2Cl_2 (300 ml) at room temperature over a period of 5 min. The reaction mixture was stirred under reflux for 3 hours, and then the solvent was removed under reduced pressure. The residue was washed twice with anhydrous ether (100 ml), and then flashed with nitrogen to remove the excess of ether. The residue obtained was dissolved in CH_2Cl_2, and a saturated aqueous solution of potassium hexafluorophosphate (KPF_6, 18.4 g, 100 mmoles) was added at room temperature with vigorous stirring for 10-15 minutes. The organic layer was collected, washed once with water (100 ml), dried over $MgSO_4$ anhydrous, filtered, the solvent removed under reduced pressure and the crude product was recrystallized from CH_2Cl_2/ether.

1,1-Dimethyl-3,3-tetramethylene-2-chloroformamidinium Hexafluorophosophate (DmTCFH**, 1c**) [12c].

The product was obtained as a white solid in yield of 82% (25.1 g), m.p. 118-119 ºC. ^{1}H nmr (CD_3CN): δ 1.98-2.04 (p, 4 H, 2 CH_2), 3.29 (s, 6 H, 2 CH_3), 3.76-3.81 (t, 4 H, 2 CH_2) ppm. ^{13}C nmr (CD_3CN): 25.66, 44.09, 55.9, 155.95. ms: m/z 161 (M^+) 163.10 (15.42, $[M+2-PF_6]^+$); 161.10 (44.38, $[M-PF_6]^+$); 70.10 (100, $[M-C_3H_6NClPF_6]^+$).

Anal. Calcd for $C_7H_{14}N_2ClPF_6$ (306.5): C, 27.56; H, 4.50; N, 9.29. Found: C, 27.40; H, 4.56; N, 9.13.

1,1-Dimethyl-3,3-pentamethylene-2-chloroformamidinium Hexafluorophosphate (DmPCFH, **1d**).

The product was obtained as a sticky solid in yield of 61% (19.7 g). ^{1}H nmr (CD_3CN): δ 1.68-1.79 (m, 6 H, 3 CH_2), 3.27 (s, 3 H, 1 CH_3), 3.28 (s, 3 H, 1 CH_3), 3.65-3.68 (m, 4 H, 2 CH_2) ppm.

Anal. Calcd for $C_8H_{16}N_2ClPF_6$ (320.5): C, 29.95; H, 4.99; N, 8.73. Found: C, 30.15; H, 5.00; N, 8.91.

General Procedure for Reaction of (**1a-e**) with *o*-Substituted Aniline.

The salt **1a-e** (5 mmoles) was added to a solution of *o*-substituted aniline **9** (5 mmoles) and triethylamine (10 mmoles) in DMF (10 ml) and the reaction mixture was refluxed for 16-24 h on a water bath. Afterwards, the mixture was left to reach room temperature, and then poured into 50 ml of cold water. The solid formed was collected by filtration and washed with water. If precipitation did not take place, the aqueous solution was extracted with dichloromethane (3x100 ml). The organic layer was collected and washed with water (50 ml), saturated NaCl (50 ml), dried $MgSO_4$, filtered and then the solvent was removed under reduced pressure. The crude product was recrystallized twice from the indicated solvent.

2-(*N, N*-Dimethyl)amino benzoxazole (**13a**).

The product was obtained as a red solid in yield of 62% (0.5 g) from ethanol, m.p. 93-95 ºC. R_f: 0.84 (CH_2Cl_2/MeOH 9:1); ir (potassium bromide): 3050-2850 (C-H), 1655 (C=N), 1590-1475 (C=C aromatic), 1270 (C-O), 1240 (C-N) cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 3.11 (s, 6 H, 2 CH_3), 6.94-6.99 (t, 1 H, aromatic), 7.02-7.14 (t, 1 H, aromatic), 7.23-7.26 (d, 1 H, aromatic), 7.35-7.38 (d, 1 H, aromatic) ppm. ^{13}C nmr (DMSO-d_6): δ 37.58, 109.03,

115.77, 120.29, 124.14, 143.85, 148.96, 163.02 ppm. ms: m/z 162 (M+): 163 (18.25, $[M+1]^+$); 162.05 (100, $[M]^+$); 161 (28.14, M-H); 147.10 (49.05, $[M-CH_3]^+$); 132.80 (27.49, $[M-C_2H_5]^+$); 119.80 (19.56, $[M-C_2H_4N]^+$); 104.05 (19.93, $[M-C_2H_4NO]^+$); 77.05 (17.24, $[M-C_3H_5N_2O]^+$); 55.10 (88.03, $[M-C_5H_3N_2O]^+$).

Anal. Calcd for $C_9H_{10}N_2O$ (162): C, 66.66; H, 6.17; N, 17.28. Found: C, 66.81; H, 6.00; N, 17.46.

2-Pyrrolidin-1-yl-benzoxazole (**13b**).

The product was obtained as a reddish brown solid in yield of 70% (0.7 g) from CH_2Cl_2/*n*-hexane, m.p. 136-138 ºC. R_f: 0.75 (CH_2Cl_2/MeOH 9:1). UV/VIS (Ethanol): λ max=210 nm (ε =20360); λ max =249 nm (ε =19310); λ max=283 nm (ε =12060). UV/VIS (CH_3CN): λ.max=209 nm (ε =23410); λ max=253 nm (ε =18960); λ max=286 nm (ε =12330). ^{1}H nmr (DMSO-d_6): δ 1.91-1.99 (p, 4 H, 2 CH_2), 3.51-3.55 (t, 4 H, 2 CH_2), 6.93-6.99 (t, 1 H, aromatic), 7.08-7.14 (t, 1 H, aromatic), 7.23-7.26 (d, 1 H, aromatic), 7.36-7.38 (d, 1 H, aromatic) ppm. ms: m/z 188 (M+): 189.25 (7.66, $[M+1]^+$); 188.15 [50.72, $[M]^+$); 187.15 (7.35, $[M-H]^+$); 161.05 (4.63, $[M-C_2H_3]^+$); 147.10 (4.70, $[M-C_3H_5]^+$); 133.05 (29.18, $[M-C_4H_7]^+$); 120.05 (3.25, $[M-C_4H_6N]^+$); 83.90 (100, $[M-C_6H_2NO]^+$); 77.05 (3.21, $[M-C_5H_7N_2O]^+$); 70.05 (14.32, $[M-C_7H_4NO]^+$); 55.10 (22.27, $[M-C_7H_5N_2O]^+$).

Anal. Calcd for $C_{11}H_{12}N_2O$ (188): C, 70.21; H, 6.38; N, 14.89. Found: C, 70.46; H, 6.20; N, 15.10.

2-Piperidin-1-yl-benzoxazole (**13c**).

The product was obtained as an orange solid in yield of 59% (0.6 g) from ethanol, m.p. 75-77 ºC. R_f: 0.89 (CH_2Cl_2/MeOH 9:1). ^{1}H nmr (DMSO-d_6): δ 1.58-1.61 (m, 6 H, 3 CH_2), 3.58-3.59 (m, 4 H, 2 CH_2), 6.98-7.00 (tt, 1 H, aromatic), 7.09-7.14 (tt, 1 H, aromatic), 7.23-7.26 (ddd, 1 H, aromatic), 7.35-7.37 (dd, 1 H, aromatic) ppm.

ms: m/z 202 (M+): 203.35 (11.58, $[M+1]^+$); 202.2 (62.87, $[M]^+$); 201.05 (12.85, $[M-H]^+$); 147.10 (35.44, $[M-C_4H_7]^+$); 133 (18.06, $[M-C_5H_9]^+$); 92 (11.40, $[M-C_6H_{10}N_2]^+$); 57.10 (100, $[M-C_8H_3N_2O]^+$); 55.10 (90.68, $[M-C_8H_7N_2O]^+$).

Anal. Calcd for $C_{12}H_{14}N_2O$ (202): C, 71.28; H, 6.93; N, 13.86. Found: C, 71.50; H, 6.85; N, 14.08.

2-(*N,N*-Dimethyl)aminobenzoimidazole (**14a**).

The product was obtained as beige-brown crystals in yield of 47% (0.37 g) from CH_2Cl_2/n-hexane, m.p. 204 ºC (dec). R_f: 0.22 (CH_2Cl_2/MeOH 9:1); ir (potassium bromide): 3120 (NH), 3060-2800 (C-H), 1645 (C=N), 1600-1575 (C=C aromatic), 1300 (C-N) cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 3.03 (s, 6 H, 2 CH_3), 6.86-6.88 (d, 2 H, aromatic), 7.13-7.16 (d, 2 H, aromatic), 11.22 (s br, 1 H, 1 NH) ppm. ^{13}C nmr (CD_3OD): δ 39.03, 113.19, 121.67, 158.62 ppm. ms: m/z 161 (M+): 162 (5.22, $[M+1]^+$); 161.10 (28.71, $[M]^+$); 160 (5.45, $[M-H]^+$); 146.05 (24.84, $[M-CH_3]^+$); 132.05 (14.48, $[M-C_2H_5]^+$); 119 (8.11, $[M-C_2H_4N]^+$); 105 (5.62, $[M-C_3H_6N]^+$); 77.15 (6.58, $[M-C_3H_6N_3]^+$); 55.10 (100, $[M-C_5H_4N_3]^+$).

Anal. Calcd for $C_9H_{11}N_3$: C, 67.08; H, 6.83; N, 26.08. Found: C, 67.31; H, 7.00; N, 26.32.

2-Pyrrolidin-1-yl-1*H*-benzoimidazole (**14b**).

The product was obtained as a beige solid in yield of 43% (0.35 g) CH_2Cl_2/n-hexane, m.p. 229 ºC (dec). R_f: 0.33 (CH_2Cl_2/MeOH 9:1). UV/VIS (Ethanol): λ max = 220 nm (ε =22900); λ max =251 nm (ε =8500); λ max =289 nm (ε =12250). ^{1}H nmr (DMSO-d_6): δ 1.92-1.96 (p, 4 H, 2 CH_2), 3.41-3.45 (t, 4 H, 2 CH_2), 6.85-6.87 (d, 2 H, aromatic), 7.12-7.15 (d, 2 H, aromatic), 11.10 (s br, 1 H, 1 NH) ppm. . ^{13}C NMR (DMSO-d_6): δ 25.43, 47.71, 111.82, 119.90, 138.29, 154.06 ppm.

Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.58; H, 6.95; N, 22.45. Found: C, 70.81; H, 7.20; N, 22.73.

2-Piperidin-1-yl-1*H*-benzoimidazole (**14c**).

The product was obtained as a pale yellow solid in yield of 44% (0.4 g) from CH_2Cl_2/n-hexane, m.p. 143 ºC (dec). R_f: 0.37 (CH_2Cl_2/MeOH 9:1). ^{1}H nmr (DMSO-d_6): δ 1.56-160 (m, 6 H, 2 CH_2), 3.45-3.48 (m, 4 H, 2 CH_2), 6.87-6.89 (d, 2 H, aromatic), 7.13-7.15 (d, 2 H, aromatic), 11.23 (s br, 1 H, 1 NH) ppm. ms: m/z 201 (M+): 201.20 (36.27, $[M]^+$); 200.20 (11.08, $[M-H]^+$); 145.95 (38.60, $[M-C_4H_7]^+$); 119 (14.57, $[M-C_5H_8N]^+$); 104 (17.78, $[M-C_5H_9N_2]^+$); 55.10 (100, $[M-C_8H_8N_3]^+$).

Anal. Calcd for $C_{12}H_{15}N_3$ (201): C, 71.64; H, 7.46; N, 20.89. Found: C, 71.80; H, 7.69; N, 21.00.

2-(*N, N*-Dimethyl)aminobenzothiazole (**15a**).

The product was purified through silica gel column using CH_2Cl_2/MeOH (9:1) as eluent, and the fractions with the same R_f values were collected and the solvent was removed *in vacuo* to give 0.4 g (44%) of the off-white solid, m.p. 90-92 ºC. R_f : 0.91 (CH_2Cl_2/ MeOH 9:1); ir (potassium bromide): 3050-2850 (C-H), 1600 (C=N), 1570-1550 (C=C aromatic), 1300 (C-N) cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 3.13 (s, 6 H, 2 CH_3), 7.00-7.05 (t, 1 H, aromatic), 7.22-7.27 (t, 1 H, aromatic), 7.41-7.44 (d, 1 H, aromatic), 7.72-7.74 (d, 1 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ 40.50, 119.14, 121.00, 121.13, 126.30, 131.52, 153.64, 169.11 ppm. ms: m/z 178 (M+): 180.15 (4.59, $[M+2]^+$); 179.10 (10.51, $[M+1]^+$); 178.10 (100, $[M]^+$); 177.15 (4.52, $[M-H]^+$); 163.05 (62.33, $[M-CH_3]^+$); 149.05 (89.76, $[M-C_2H_5]^+$); 136.05 (35.53, $[M-C_2H_4N]^+$); 121.80 (1.26, $[M-C_3H_6N]^+$); 107.85 (12.54, $[M-C_3H_6N_2]^+$); 55.10 (5.13, $[M-C_5H_3N_2S]^+$).

*Ana*l. Calcd for $C_9H_{10}N_2S$ (178): C, 60.67; H, 5.61; N, 15.73. Found: C, 60.89; H, 5.43; N, 15.96.

2-Pyrrolidin-1-yl-benzothiazole (**15b**).

The product was purified through silica gel column using CH_2Cl_2/MeOH (9:1) as eluent, and the fractions with the same R_f values were collected and the solvent was removed *in vacuo* to give 0.5 g (48%) of the off-white solid, m.p. 101-103 ºC. R_f: 0.89 (CH_2Cl_2/MeOH 9:1). UV/VIS (Ethanol): λ max =225 nm (ε =24830); λ max =271 nm (ε =15160). ^{1}H nmr (DMSO-d_6): δ 1.97-2.02 (p, 4 H, 2 CH_2), 3.45-3.50 (t, 4 H, 2 CH_2), 6.99- 7.04 (t, 1 H, aromatic), 7.22-7.27 (t, 1 H, aromatic), 7.42-7.45 (d, 1 H, aromatic), 7.72-7.74 (d, 1 H, aromatic) ppm. ms: m/z 204 (M+): 206.10 (5.07, $[M+2]^+$); 205.10 (14.14, $[M+1]^+$); 204.10 (100, $[M]^+$); 203.10 (11.49, $[M-H]^+$); 177.05 (11.75, $[M-C_2H_3]^+$); 163 (10.87, $[M-C_3H_5]^+$); 149 (64.77, $[M-C_4H_7]^+$); 136 (6.87, $[M-C_4H_6N]^+$); 121.95 (1.42, $[M-C_5H_8N]^+$); 107.95 (8.69, $[M-C_5H_8N_2]^+$); 55.10 (2.70, $[M-C_7H_5N_2S]^+$).

Anal. Calcd for $C_{11}H_{12}N_2S$ (204): C, 64.70; H, 5.88; N, 13.72. Found: C, 64.99; H, 5.61; N, 13.98.

N''-(2-Aminophenyl)-*N,N,N',N'*-tetramethylguanidinium hexafluorophosphate (**12a**).

The product was obtained as a white solid in 34% yield (0.35 g), m.p. 124-125 ºC. R_f: 0.39 (CH_2Cl_2/ MeOH 9:1). ir

(potassium bromide): 3480 (NH), 3390-3360 (NH_2), 3050-2900 (C-H), 1640 (C=N), 1565-1510 (C=C aromatic), 1310 (C-N) cm^{-1}. ^1H nmr (DMSO-d_6): δ 2.86 (s, 12 H, 4 CH_3), 5.19 (s, 2 H, 1 NH_2), 6.56-6.62 (t d, 1 H, aromatic), 6.74-6.80 (m, 2 H, aromatic), 6.98-7.04 (t d, 1 H, aromatic), 9.03 (s br, 1 H, 1 NH) ppm. ^{13}C nmr (DMSO-d_6): δ 34.72, 116.32, 117.34, 119.86, 124.79, 127.76, 142.63, 160.09 ppm.

Anal. Calcd for $C_{11}H_{19}F_6N_4P$ (352.3): C, 37.51; H, 5.44; N, 15.90. Found: C, 37.69; H, 5.58; N, 16.13.

N''-[(2-Aminophenylamino)-*N*,*N*-dimethyl-*N*',*N*'-tetramethylene-guanidiniumhexa-fluorophosphate (**12b**).

The product was obtained as an off white solid in 27% yield (0.3 g), m.p. 134-136 ºC. R_f : 0.50 (CH_2Cl_2/ MeOH 9:1). ^1H nmr (DMSO-d_6): δ 1.85-1.87 (m, 4 H, 2 CH_2), 2.72 (s, 3 H, 1 CH_3), 2.84 (s, 3 H, 1 CH_3), 3.44-3.46 (m, 4 H, 2 CH_2), 5.17 (s, 2 H, 1 NH_2), 6.56-6.62 (t d, 1 H, aromatic), 6.76-6.79 (d d, 1 H, aromatic), 6.81-6.84 (d d, 1 H, aromatic), 6.98-7.04 (t d, 1 H, aromatic), 8.81 (s br, 1 H, 1 NH) ppm.

Anal. Calcd for $C_{13}H_{21}F_6N_4P$ (378.3): C, 41.27; H, 5.60; N, 14.81. Found: C, 41.43; H, 5.68; N, 14.99.

General Procedure for the Reaction of *N*,*N*-Dimethyl Carbamoyl Chloride with *o*-Substituted Aniline.

N,*N*-Dimethylcarbamoyl chloride **14** (5.5 ml, 60 mmoles) was added to a mixture of *o*-substituted aniline **9** (50 mmoles) and triethylamine (13.9 ml, 100 mmoles) in DMF (50 ml). The reaction mixture was refluxed for 12-18 h. After cooling, the reaction mixture was poured into 100 ml of water. The solid was collected by vacuum filtration, and then washed with water. The crude product was recrystallised from 1,4-dioxane. The aqueous layer was extracted with 200 ml of CH_2Cl_2. Then the organic layer was washed with 100 ml of water, dried over anhydrous $MgSO_4$. The solvent was removed under high pressure. The crude product was crystallized from CH_2Cl_2/*n*-hexane.

Benzoxazol-2-ol (**18a**).

The product was obtained as brown solid in 15% yield (1 g), m.p. 130-132 ºC. R_f : 0.66 (CH_2Cl_2/MeOH 9:1); ir (potassium bromide): 3500 (-OH), 3100-3050 (C-H), 1640 (C=N), 1600-1475 (C=C aromatic), 1310 (C-O), 1260 (C-N) cm^{-1}. ^1H nmr ($CDCl_3$): δ 3.48 (s br, 1 H, 1 OH), 7.03-7.16 (m, 3 H, aromatic), 7.25-7.28 (d d, 1 H, aromatic) ppm. ^{13} C-NMR (DMSO-d_6): δ 109.80, 110.20, 122.38, 124.22, 130.33, 143.53, 155.05 ppm. ms: m/z 135 (M+): 135 (100, $[M]^+$); 84 (19.53, $[M-C_4H_3]^+$); 53.10 (11.08, $[M-C_3NO_2]^+$).

Anal. Calcd for $C_7H_5NO_2$(135.12): C, 62.22; H, 3.73; N, 10.37. Found: C, 62.34; H, 3.79; N, 10.49.

1,3-Dihydrobenzoimidazol-2-one (**18b**).

The product was obtained as white crystals in 32% yield (2 g), m.p. 240 ºC (dec). R_f: 0.50 (CH_2Cl_2/MeOH 9:1); ir (potassium bromide): 3170 (NH), 3100-3050 (C-H), 1760 (C=O), 1630-1480 (C=C aromatic), 1265 (C-N) cm^{-1}. ^1H nmr (DMSO-d_6): δ 6.91 (s, 4 H, aromatic), 10.57 (s, 2 H, 2 NH) ppm. ^{13}C NMR (DMSO-d_6): δ 107.44, 119.36, 128.02, 154.12 ppm. ms: m/z 135 (M+): 135 (9.44, $[M+1]^+$); 134.05 (100, $[M]^+$); 132.95 (10.72, $[M-H]^+$); 53 (13.64, $[M-C_3HN_2O]^+$).

Anal. Calcd for $C_7H_6N_2O$ (134.14): C, 62.68; H, 4.51; N, 20.88. Found: C, 62.79; H, 4.59; N, 21.00.

The product from the aqueous layer was obtained as a white solid in yield 2% (0.2 g), m.p.155-157 ºC. R_f : 0.27 (CH_2Cl_2/ MeOH 9:1). ^1H nmr (DMSO-d_6): δ 2.99 (s, 3 H, 1 CH_3), 3.03 (s, 3 H, 1 CH_3), 7.08-7.12 (m, 4 H, aromatic), 11.14 (s, 1 H, 1 NH) ppm. This compound was identified as 2-(*N*,*N*-dimethyl)amino-benzoimidazole **14a**.

S-(2-aminophenyl)-*N*,*N*-dimethylthiocarbamate (**19**).

The product was obtained as white needles in 30 % yield (3 g), m.p. 62-64 ºC. R_f: 0.93 (CH_2Cl_2/MeOH 9:1); ir (potassium bromide): 3440-3340 (NH_2), 3080-2950 (C-H), 1660 (C=O), 1580-1480 (aromatic), 1260 (C-N) cm^{-1}. ^1H nmr (DMSO-d_6): δ 2.90 (d, 3 H, 1 CH_3), 3.05 (d, 3 H, 1 CH_3), 5.26 (s, 2 H, 1 NH_2), 6.49-6.54 (t d, 1 H, aromatic), 6.71-6.74 (d d, 1 H, aromatic), 7.09-7.13 (m, 2 H, aromatic) ppm. ^{13}C nmr (DMSO-d_6): δ 36.89, 110.35, 115.35, 117.17, 131.51, 138.01, 150.79, 165.65 ppm. ms: m/z 196 (M+): 196.15 (11.10, $[M]^+$); 104 (8.42, $[M-C_6H_6N]^+$); 72.05 (100, $[M-C_6H_6NS]^+$); 55.05 (100, $[M-C_5H_5N_2OS]^+$); 53.10 (3.79, $[M-C_5H_7N_2OS]^+$).

Anal. Calcd for $C_9H_{12}N_2OS$ (196.3): C, 55.08; H, 6.16; N, 14.27. Found: C, C, 55.28; H, 6.19; N, 14.32.

General Procedure for Reaction of **1a-e** with Hydrazine Derivatives.

The salt **1a-e** (5 mmoles) was added to a solution of hydrazine derivatives (5 mmoles) and triethylamine (10 mmoles) in DMF (10 ml) and the reaction mixture was stirred at room temperature overnight. Afterwards, the mixture was left to reach room temperature, and then poured into 50 ml of cold water. The solid formed was filtered directly and washed with water. If precipitation did not take place, the aqueous solution was extracted with dichloromethane (3x100 ml). The organic layer was collected and washed with water (50 ml), saturated NaCl (50 ml), dried $MgSO_4$, filtered and then the solvent was removed under reduced pressure. The crude product was recrystallized from the indicated solvent.

4-Benzyl-1-(*N*,*N*-dimethylamino)-[1,2,4]triazolo[4,3-*a*]quinoxaline (**6a**) [10].

The product was obtained as an orange solid in 61% yield (0.9 g) from ethanol, m.p. 166-167 ºC. R_f: 0.83 (CH_2Cl_2/MeOH 9:1); ir (potassium bromide): 3100-2900 (C-H), 1620 (C=N), 1540-1500 (C=C aromatic), 1480 (-CH_2-), 1300 (C-N) cm^{-1}. ^1H nmr (DMSO-d_6): δ 2.93 (s, 6 H, 2 CH_3), 4.48 (s, 2 H, 1 CH_2), 7.20-7.27 (t t, 1 H, aromatic), 7.29-7.32 (m, 2 H, aromatic), 7.45-7.48 (d d, 2 H, aromatic), 7.59-7.64 (td, 1 H, aromatic), 7.67-7.73 (td, 1 H, aromatic), 7.96-7.99 (dd, 1 H, aromatic), 8.41-8.45 (dd, 1 H, aromatic) ppm. ms: m/z 303 (M+): 304.15 (14.98, $[M+1]^+$); 303.20 (61.11, $[M]^+$); 302.20 (50.96, [M-H]); 274.05 (15.28, $[M-C_2H_5]^+$); 233.10 (19.64, $[M-C_3H_6N_2]^+$); 77.10 (7.05, $[M-C_{12}H_{12}N_5]^+$); 55.15 (100, $[M-C_{14}H_{10}N_5]^+$).

4-Benzyl-1-pyrrolidin-1-yl-[1,2,4]triazolo[4,3-*a*]quinoxaline (**6b**)[10].

The product was obtained as beige solid in 83% yield (1.4 g) C from ethanol, m.p. 144-145 ºC. R_f : 0.86 (CH_2Cl_2/MeOH 9:1). UV/VIS (Ethanol): λ max =219 nm (ε = 21050); λ max=260 nm (ε=13410); λ max =327 nm (ε=5290). UV/VIS (CH_3CN): λ max =207 nm (ε=23560); λ max = 258 nm (ε=13020); λ max =327 nm (ε=4970); ir (potassium bromide): 3100-2860 (C-H), 1620 (C=N), 1525-1500 (C=C aromatic), 1460 (-CH_2-), 1300 (C-N)

cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.07-2.12 (p, 4 H, 2 CH_2), 3.51-3.55 (t, 4 H, 2 CH_2), 4.59 (s, 2 H, 1 CH_2), 7.21-7.23 (m, 1 H, aromatic), 7.27-7.32 (m, 2 H, aromatic), 7.53-7.57 (m, 2 H, aromatic), 7.64-7.66 (m, 2 H, aromatic), 8.00-8.04 (m, 1 H, aromatic), 8.36-8.39 (m, 1 H, aromatic) ppm. ^{13}C nmr ($CDCl_3$)**:** δ 24.75, 40.24, 51.91, 116.00, 126.73, 126.77, 128.15, 128.40, 129.60, 129.75, 136.44, 136.70, 142.89, 154.50, 155.50 ppm. ms: m/z 329 (M+): 330.25 (7.49, $[M+1]^+$); 329.25 (26.85, $[M]^+$); 328.20 (14.96, $[M-H]^+$); 302.25 (9.58, $[M-C_2H_3]^+$); 274.20 (14.33, $[M-C_4H_8]^+$); 232.20 (13.43, $[M-C_5H_9N_2]^+$); 219.10 (7.05, $[M-C_5H_8N_3]^+$); 83.95 (100, $[M-C_{15}H_9N_4]^+$); 70.10 (33.38, $[M-C_{16}H_{11}N_4]^+$); 55.10 (40.39, $[M-C_{16}H_{12}N_5]^+$).

3-Pyrrolidin-1-yl-[1,2,4]triazolo[3,4-*a*]phthalazine (**7a**) [10].

The product was obtained as deep yellow solid in 66% yield (0.8 g) from CH_2Cl_2/*n*-hexane, m.p. 119 ºC (dec). R_f: 0.65 (CH_2Cl_2/MeOH 9:1); UV/VIS (Ethanol): λ max = 217 nm (ε = 25590); λ max = 278 nm (ε = 20170); λ max = 321 nm (ε = 4420);ir (potassium bromide): 3100-2880 (C-H), 1610 (C=N), 1590-1550 (C=C aromatic), 1475 (-CH_2-), 1340 (C-N) cm^{-1}. ^1H nmr (DMSO-d_6): δ 2.02-2.06 (p, 4 H, 2 CH_2), 3.82-3.87 (t, 4 H, 2 CH_2), 7.96-8.07 (m, 2 H, aromatic), 8.14-8.18 (d, 1 H, aromatic), 8.32-8.36 (d, 1 H, aromatic), 8.99 (s, 1 H, 1 CH) ppm. ^{13}C nmr (DMSO-d_6): δ 22.88, 47.75, 119.27, 120.52, 121.49, 127.49, 130.83, 132.88, 137.20, 143.54, 146.45 ppm. ms: m/z 239 (M+): 239.15. MS (EI): 239.15 (5.06, $[M]^+$); 184.15 (7.13, $[M-C_4H_7]^+$); 169.10 (7.14, $[M-C_4H_8N]^+$); 57.15 (100, $M-C_9H_4N_5]^+$); 55.10 (49.81, $[M-C_9H_6N_5]^+$).

3-Piperidin-1-yl-[1,2,4]triazolo[3,4-*a*]phthalazine (**7b**) [10].

The product was obtained as yellow solid in 70% yield (0.9 g) from ethanol, m.p. 130 ºC. R_f: 0.61 (CH_2Cl_2/MeOH 9:1). ^1H nmr (DMSO-d_6): δ 1.60 - 1.67 (m, 6 H, 3 CH_2), 3.47-3.5 (t, 4 H, 2 CH_2), 7.77-7.82 (t, 1 H, aromatic), 7.91-7.96 (t, 1 H, aromatic), 8.05-8.08 (d, 1 H, aromatic), 8.31-8.34 (d, 1 H, aromatic), 8.83 (s, 1 H, 1 CH) ppm. ^{13}C NMR (DMSO-d_6): δ 21.83, 22.80, 46.90, 119.48, 120.30, 121.32, 126.79, 128.36, 131.98, 138.44, 144.48, 150.78 ppm.

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