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Synthesis of Novel Angular Diazaphenoxazinone Derivatives *via* Palladium Catalyzed Buchwald-Hartwig Amidation Protocols

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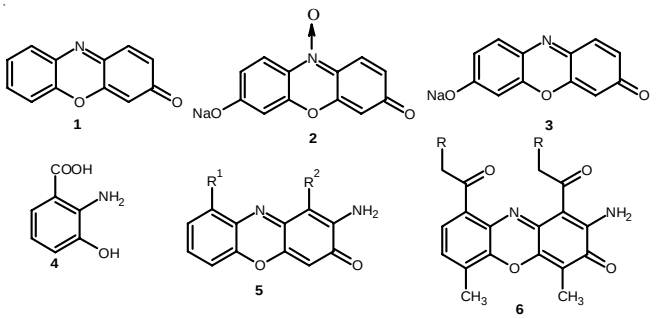
The synthesis of new amido derivatives of angular diazaphenoxazinone *via* tandem amidation protocol is reported. This was achieved by the condensation of 4,5-diamino-6-hydroxypyrimidine (**7**) with 2,3-dichloro-1,4-naphthoquinone (**8**) in anhydrous basic medium to furnish the key intermediate, 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazin-5-one (**9**). Palladium catalyzed amidation reaction of 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazin-5-one (**9**) with different amides (**12a-c**) (benzamide, acetamide, salicylamide and 4-nitrobenzamide) in the presence of palladium(II) acetate, triphenyl phosphine (PPh_3), water and tertiary butanol at 110 °C for 3 h gave the new amido derivatives **13a-c**. Structures of the new compounds were established by elemental analysis, UV, FTIR, ^{1}H NMR and ^{13}C NMR.

Keywords: Synthesis, Phenoxazines, Phenoxazinone, Diazaphenoxazinone, Tandem catalysis.

INTRODUCTION

Phenoxazinones are coplanar, tricyclic compounds containing two or even more additional functional groups (R) from amino-, oxygen-, benzene-, sulfonic-, methyl-, ethyl- and hydroxyl-substituents[1]. The phenoxazinone core (**1**) has been found in various biological systems including pigments produced by diverse organisms such as insects[2], fungi[3] and Australian marsupials[4]. It seems to participate in a mechanism to protect mammalian tissue from oxidative damage[5] and forms the core structure of certain antibiotics. It is also considered to contribute to the activity of phenoxazinone antibiotics, allowing the compounds to intercalate nucleic acids, in which so many phenoxazinones are effective anticancer agents[6]. The core structure is also found in the dyes resazurin (**2**) and resorufin (**3**)[7] and some phenoxazinone compounds are used as substrate probes for the detection of enzymes[8] and the amplification of the antibiotic activity of other antibiotics[9]. Phenoxazinones have also been detected as by-products in the growth medium of *Pseudomonas putida* strain TW3, when the strain was grown on 4-nitro-substituted substrates[10]. It is therefore not surprising that various enzymes have been reported to be involved in the production of the core structure. One example from nature is 3-hydroxyanthranilic acid (3-HAA) (**4**), which is the precursor of the laccase-catalyzed formation of the phenoxazinone derivative cinnabarinic acid (**5**) in the fungus *Pycnoporus cinnabarinus*[6,11]. Dactinomycin also known generically as actinomycin D (**6**) is the most significant member of actinomycines which are a class of polypeptide antibiotics isolated from soil bacteria. Phenoxazines have been reported to show interesting anti-inflammatory[12], multi drug resistance reversal activity[13], prevent human amyloid disorder[14], protect neuronal cells from death by oxidative stress[15], antitumor[16], antimicrobial[17], and antiviral activities[18]. Zuse *et al.*[19] reported 9-benzylidene-naphtho[2,3-b]thiophen-4-ones as novel antimicrotubule agent. Prinz *et al.*[20] reported *N*-benzoylated phenoxazines as inhibitors of tubulin polymerization which implies that the compounds are potential anticancer agent. Nowakowska-Oleksy *et al.*[21] reported phenoxazine-based conjugates of semiconducting and luminescent properties. Raju *et al.*[22] reported the facile synthesis of phenoxazines *via* ring opening of benzoxepines. Thome *et al.*[23] reported the transition-metal-free synthesis of *N*-substituted phenoxazines from *N*-acetylated aryloxy anilides. Reddy[24] reported an improved process for the synthesis of phenoxazine with antidiabetic properties. Jose and Burgess[25] reported the synthesis of benzophenoxazine-based fluorescent dyes for labeling biomolecules. Hayashi *et al.*[26] reported phenoxazine derivatives that could suppress infections caused by herpes simplex virus type-1 and herpes simplex virus type-2. Shimamoto *et al.*[27] reported novel phenoxazine derivatives with *in vitro* and *in vivo* antitumor effect on human leukemia cell lines. Iwata *et al.*[28] reported phenoxazine derivatives of ability to suppress proliferation of poliovirus and porcine parvovirus. Idries and Abeed[29] synthesized 10*H*-substituted

phenoxazine-3-yl-6-pyrimidin-2-phenylthiol/ol/amine/thiol pyrroles using 2-[4-hydroxybenz-1(propene-1-one)]pyrrole. Frade *et al.*[30] reported benzo[a]phenoxazine heterocycles with antimicrobial activity. Persson[31] reported the synthesis of non-conjugate potential-stepping phenothiazine and phenoxazine based polymer hole-transport material for dye-sensitized solar cells. Kohli *et al.*[32] reported 5-(2-aryl-4-oxo-1,3-thiazolidine)-2-(phenoxa-zinylmethyl)-1,3,4-thiadiazole derivatives with anti-tubercular activity. Pereira *et al.*[33] reported benzo[a]phenoxazinium chlorides used in *Candida albicans* inactivation by photodynamic therapy. Quite a number of researchers have reported varieties of methodologies for the synthesis of phenoxazinone. Gomes *et al.*[34] reported the synthesis of pitucamycin, a structural merger of a phenoxazinone with an epoxyquinone antibiotics. Tomoda *et al.*[35] reported the conversion of 2-amino-5-methylphenol to the dihydrophenoxazinone derivatives with reddish brown colour using purified human hemoglobin, lysates of human erythrocytes or human erythrocytes. Hassanein *et al.*[36] repoted the synthesis of phenoxazinones *via* cobalt(I) phthalocyanine tetrasodium sulfonate catalyzed molecular oxygen oxidation of 2-aminophenol. Kaizer *et al.*[37] reported the synthesis of 2-aminophenoxazin-3-one using 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) initiated oxidation of 2-aminophenol. Forte *et al.*[38] reported the synthesis of novel phenoxazinone dye using luccase action on 3-amino-4-hydroxybenzenesulphonic acid. Maurya *et al.*[39] reported the biomimetic oxidative coupling of 2-aminophenol to 2-amino-phenoxazin-3-one using *bis*(2-[α-hydroxyethyl]benzimidazolato) copper(II) anchored onto chloromethylated polystyrene. Hayakawa *et al.*[40] reported the successful oxidation of benzo[a]phenoxazine with ethanolic ferric chloride to obtain benzo[a]phenoxazin-5-one, indicating that the position 5 is the center which is most susceptible to oxidization. Hayakawa *et al.*[40] prepared 1-substituted-6-halogenobenzo[a]-11-azaphenoxazin-5-one and 4-substituted-6-halogeno-benzo[a]-11-azaphenoxazin-5-one by simple condensation of 2-amino-3-hydroxypyridine with 2,3-dihalogeno-1,4-naphthoquinone in ethanolic-benzene in the presence of anhydrous potassium acetate. In view of the interesting pharmacological applications of this class of compound we report in this work the palladium catalyzed synthesis of angular diazaphenoxazinone *via* Buchwald-Hartwig amidation reaction.



EXPERIMENTAL

Melting points of the compounds were determined using electro-thermal melting point apparatus in open capillaries and are uncorrected. Ultra violet and visible spectra were recorded on a UNICO-UV 2500PC series spectrophotometer at (National Research Institute for Chemical Technology, Zaria) using matched 1 cm quartz cells. The absorption maxima were given in nanometer (nm). Fourier Transform Infrared spectral data were recorded on FTIR 8400S using KBr disc. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) was determined using Varian NMR Mercury-200BB Spectrophotometer (Obafemi Awolowo University, Ile-Ife). Chemical shifts were reported in δ (neat). Analytical samples were obtained by column chromatography on silica gel (Merck 70-325 mesh ASTM) by employing methanol and acetone (2:1) as eluent followed by recrystallization. The elemental analysis was done on a Heraeus CHN-O rapid analyzer. The molecular masses of the compounds were determined by GCMS-QP2010 PLUS SCHIMADZU, Japan. All the reagents were of analytical grade and purchased from Sigma-Aldriech Germany and used without further purification.

11-Amino-6-chloro-8,10-diazabenzo[a]phenoxazin-5-one(9): 4,5-Diamino-6-hydroxypyrimidine (0.56 g), sodium acetate (0.36 g) and benzene (60 mL) mixed with dimethyl formamide (30 mL) were charged into 250 mL two-necked round bottomed flask fitted with short magnetic stirring bar and a reflux condenser. The mixture was stirred while heating on a water bath at 70-75 °C for 45 min. Thereafter, 2,3-dichloro-1,4-naphthoquinone (1 g) was added and the stirring continued with heating at 70-75 °C for 8 h. The colour of the reaction mixture changed from light brownish green to yellow red and intense red as the reaction progressed. At the end of the 8 h, the reaction mixture was filtered and cooled in ice overnight and filtered again to give the solid compound. Analytical sample was obtained by column chromatography using benzene as the eluting solvent followed by recrystallization to obtain the target compound; Yield 4.80 g, (55 %); m.p. 293 °C; the literature melting point (290 °C), UV-visible (benzene) λ_{max}: 465 nm. IR (KBr, ν_{max}, cm^{-1}): 3500 and 3350 (NH_2), 2932 (Ar-H), 1678 (C=O), 1350 (aromatic C-N), 1265 (C-O-C), 733 (C-Cl). ^{1}H NMR ($CDCl_3$): δ 8.3 (m, 4H, Ar-H), 7.9 (s, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 170.20, 142.81, 139.85, 135.45, 134.09, 132.10, 131.32, 130.29, 128.50, 125.27, 123.38, 117.86, 110.20.

Reduction of 11-amino-6-chloro-8, 10-diazabenzo[a]-phenoxazin-5-one (10): 11-Amino-8,11-diazabenzo[a]phenoxazin-5-one (0.56 g, 0.0044 mol), sodium dithionite (2 g, 0.0044 mol), acetone (25 mL) and 2 drops of DMSO were put in 100 mL two necked round bottom flask and refluxed for 0.5 h. Water (5 mL) was added and the reddish colour changed immediately to light yellow and subsequently colourless. This colourless solution then changed back to red on exposure to air. The product precipitated with water, isolated and found to be 11-amino-6-chloro-8,10-diazabenzo[a]-phenoxazin-5-one by instrumental analysis.

Procedure for amide synthesis: This preparation was carried out in a fume cupboard. Carboxylic acids (10 g) were heated with 30 g (excess) of thionyl chloride on a boiling water bath for 3 min. under reflux. Thereafter the mixture was heated for further 10 min. The solution was gradually cooled to 0 °C and 150 mL of concentrated ammonia was added in drops. The product was filtered and recrystallized from water. The amides prepared include salicylamide (m.p. 144-145 °C), the literature (m.p. 140-144 °C), yield (4.40 g, 44 %), UV-visible (methanol) λ_{max}: 298.4 nm; benzamide (m.p. 129-130 °C), the

literature (m.p. 128-129 °C), yield (6.10 g, 61 %), UV-visible (methanol) λ_{max}: 287 nm and 4-nitrobenzamide (m.p. 248-249 °C), the literature (m.p. 245-248 °C), yield (5.10 g, 51 %), UV-visible (methanol) λ_{max}: 357.4 nm.

11-Amino-6-acetamido-8,10-diazabenzo[a]phenoxazin-5-one (13a): This compound was prepared by heating palladium acetate (67 mg, 0.015 mmol), water (0.06 mmol) and triphenylphosphine (0.045 mmol) for 1.5 min at 110 °C in *t*-butanol to give a highly active catalyst Pd(0). Thereafter, potassium phosphate (180 mg, 1 mol), acetamide (49 mg, 1 mol) and 11-amino-6-chloro-8,10-diazabenzo[a]-pheno-xazin-5-one (250 mg, 1 mol) were added and refluxed for 3 h to give orange red solution. The solution was filtered and the filtrate allowed to evaporate to dryness and the residue recrystallized with a mixture of methanol and acetone (2:1) to obtain 11-amino-6-ethanamido-8,10-diazabenzo[a]phenoxazin-5-one as a brick red solid. Yield 1.8 g (16.83 %), m.p. 320 °C, m.w. 321.29. Elemental analysis of $C_{16}H_{11}N_5O_3$ (calcd.): C 59.81, H 3.45, N 21.80; found: C 59.72, H 3.50, N 21.72. UV-visible (acetone, λ_{max}): 482 nm, FTIR (KBr, ν_{max}, cm^{-1}): 3452, 3200 (NH_2), 3057 (Ar-H), 1685, 1679 (2C=O), 1432 (aromatic C-N), 1264(C-O), 734 (substitution in benzene). ^{1}H NMR (DMSO): δ 7.78 (m, 4H, Ar-H), 1.85 (s, 3H, CH_3). ^{13}C NMR (DMSO): δ 169, 160, 154, 152, 148, 142, 137, 135, 134, 131, 128, 125.88, 125.65, 120, 111, 41.

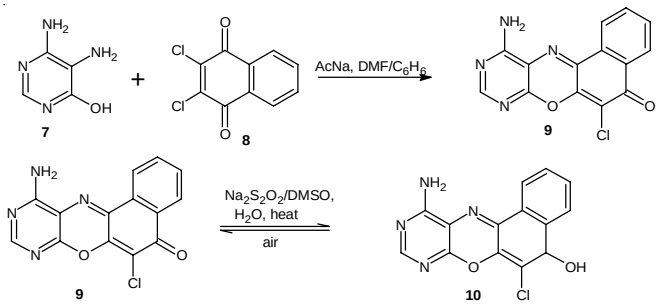
11-Amino-6-benzamido-8,10-diazabenzo[a]phenoxazin-5-one (13b): A mixture of palladium acetate (67 mg, 0.015 mmol), water (0.06 mmol) and triphenylphosphine (89 mg, 0.045 mmol) were heated for 1.5 min at 110 °C in *t*-butanol to give a highly active catalyst Pd(0) in a greenish-light yellow solution. Thereafter, potassium phosphate (180 mg, 1 mol), benzamide (41 mg, 1 mol) and 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazin-5-one (250 mg, 1 mol) were added and refluxed for 3 h at 110 °C to give a reddish solution. The solution was filtered and the filtrate allowed to evaporate to dryness, the product was recrystallized from a mixture of acetone and methanol (1:2) to obtain 11-amino-6-benzamido-8,10-diazabenzo[a]phenoxazin-5-one as a brick red solid. Yield (11 %), m.p. > 300 °C, m.w. 383.35. Elemental analysis of $C_{21}H_{13}N_5O_3$ (calcd.): C 5.79, H 3.42, N 18.29; found: C 65.80, H 3.40, N 18.45. UV-visible (acetone, λ_{max}): 468 nm. FTIR (KBr, ν_{max}, cm^{-1}): 3360, 3171 (NH_2), 1680, 1644 (C=O), 1397 (aromatic C-N), 1125 (C-O), 775 (substitution in benzene ring). ^{1}H NMR ($CDCl_3$): δ 7.9 (m, 5H, Ar-H), 7.5 (m, 4H, Ar-H), 7.4 (s, 1H, Ar-H), 6.4 (s, 1H, NH), 2.5 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): δ 171, 170, 152, 148, 145, 142, 140.25, 139.30, 138.04, 137.97, 137.20, 134.56, 132.98, 132.25, 131.08, 130.28, 129.39, 128.60, 127.09, 126.90, 118.89.

11-Amino-6-(2-hydroxybenzamido)-8,10-diazabenzo-[a]phenoxazin-5-one (13c): This compound was obtained by heating palladium acetate (68 mg, 0.015 mmol), water (0.06 mmol) and triphenylphosphine (89 mg, 0.045 mmol) for 1.5 min at 110 °C in *t*-butanol to give a highly active catalyst Pd(0). Potassium phosphate (180 mg, 1 mol), salicylamide (117 mg, 1 mol) and 11-amino-6-chloro-8,10-diaza-benzo[a]phenoxazin-5-one (250 mg, 1 mol) were added to the pre-activated catalyst and refluxed for 3 h at 110 °C to give a reddish solution. The solution was filtered and the solvent evaporated to obtain the crude product which was recrystallized from acetone and methanol (1:2) to give 11-amino-6-(2-hydroxybenzamido)-8,10-diazabenzo[a]phenoxazin-5-one as a reddish solid. Yield 14.71 %, m.p 310 °C, m.w. 399.35. Elemental analysis of $C_{21}H_{13}N_5O_4$ (calcd.): C 63.16, H 3.28, N 17.54; found: C 63.20, H 3.31, N 17.48. UV-visible (acetone, λ_{max}): 480.5 nm. FTIR (KBr, ν_{max}, cm^{-1}): 3377, 3200 (NH_2), 3180 (b, OH), 3000 (Ar-H), 1690, 1641 (C=O), 1570 (C=C), 1150 (C-O). ^{1}H NMR (DMSO): δ 8.1 (m, 4H, Ar-H), 7.5 (m, 4H, Ar-H). ^{13}C NMR (DMSO): δ 170.03, 168.358, 153.34, 152.90, 149.08, 148.37, 143.21, 140.27, 136.45, 135.94, 134.69, 133.86, 131.07, 131.66, 130.45, 128.85, 127.89, 125.63, 120.34, 117.32, 110.65.

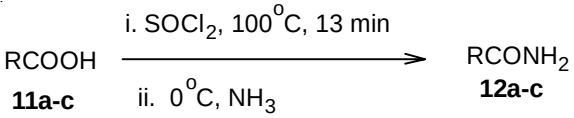
11-Amino-6-(4-nitrobenzamido)-8,10-diazabenzo[a]-phenoxazin-5-one (13d): This compound was prepared by heating palladium acetate (67 mg, 0.015 mmol), water (0.06 mmol) and triphenylphosphine (89 mg, 0.045 mmol) for 1.5 min at 110 °C in *t*-butanol to give a highly active catalyst Pd(0) as a greenish-light yellow solution. Potassium phosphate (180 mg, 1 mol), 4-nitrobenzamide (138 mg, 1 mol) and 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazin-5-one (250 mg, 1 mol) were added to the solution and refluxed for 3 h at 110 °C to give a reddish solution. The solution was filtered and the solvent evaporated using rotary evaporator. The product was recrystallized from a mixture of acetone and methanol (1:2) to obtain 11-amino-6-(4-nitrobenzamido)-8,10-diazabenzo[a]-phenoxazinone as an orange red solid. Yield 13.17 %, m.p. 330-331 °C, m.w. 428.35. Elemental analysis of $C_{21}H_{12}N_6O_5$ (calcd.): C 58.88, H 2.82, N 19.62; found: C 58.57, H 2.90, N 20.03. UV-visible (acetone λ_{max}): 480 nm. FTIR (KBr, ν_{max}, cm^{-1}): 3500, 3460 (NH_2), 3056, 3000 (Ar-H), 1680, 1659 (2C=O), 1600 (C=C), 1550 (C=N), 1263 (C-O), 734 (substitution in benzene ring). ^{1}H NMR (DMSO): δ 8.4 (m, 4H, Ar-H), 7.5 (m, 4H, Ar-H). ^{13}C NMR (DMSO): δ 170.51, 168.73, 153.35, 151.56, 149.90, 148.20, 147.78, 139.98, 138.98, 138.60, 137.85, 137.02, 135.91, 135.12, 132.22, 131.01, 130.90, 126.99, 124.06, 123.55, 119.20.

RESULTS AND DISCUSSION

The reaction of 4,5-diamino-6-hydroxypyrimidine (**7**) and 2,3-dichloro-1,4-naphthoquinone (**8**) afforded the key intermediate 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazinone (**9**) (**Scheme-I**). The benzamides (**12a-c**) was synthesized by the simultaneous reaction of benzoic acids (**11a-c**), thionyl chloride and concentrated ammonia (**Scheme-II**). The palladium catalyzed Buchwald-Hartwig reaction of 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazinone (**9**) and amides (acetamide and benzamides **12a-c**) afforded the amide derivatives of angular diazaphenoxazinone (**13a-d**) (**Scheme-III**). The UV results revealed an increased wavelength of maximum absorption which is implicated by the increased conjugation in the amide derivatives when compared with the intermediate. Although not much change is expected from the FTIR, the presence of two carbonyl bands in the amide derivatives is diagnostic. The two carbonyl peaks observed in the carbon-13 NMR and the elemental analysis further proved the successful synthesis of the angular diazaphenoxazinone derivatives reported.

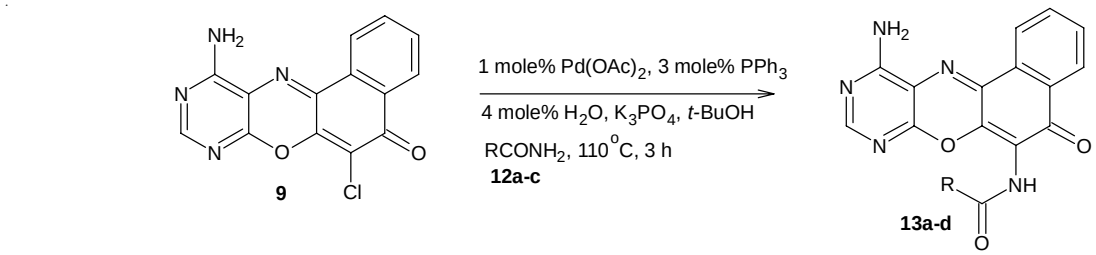


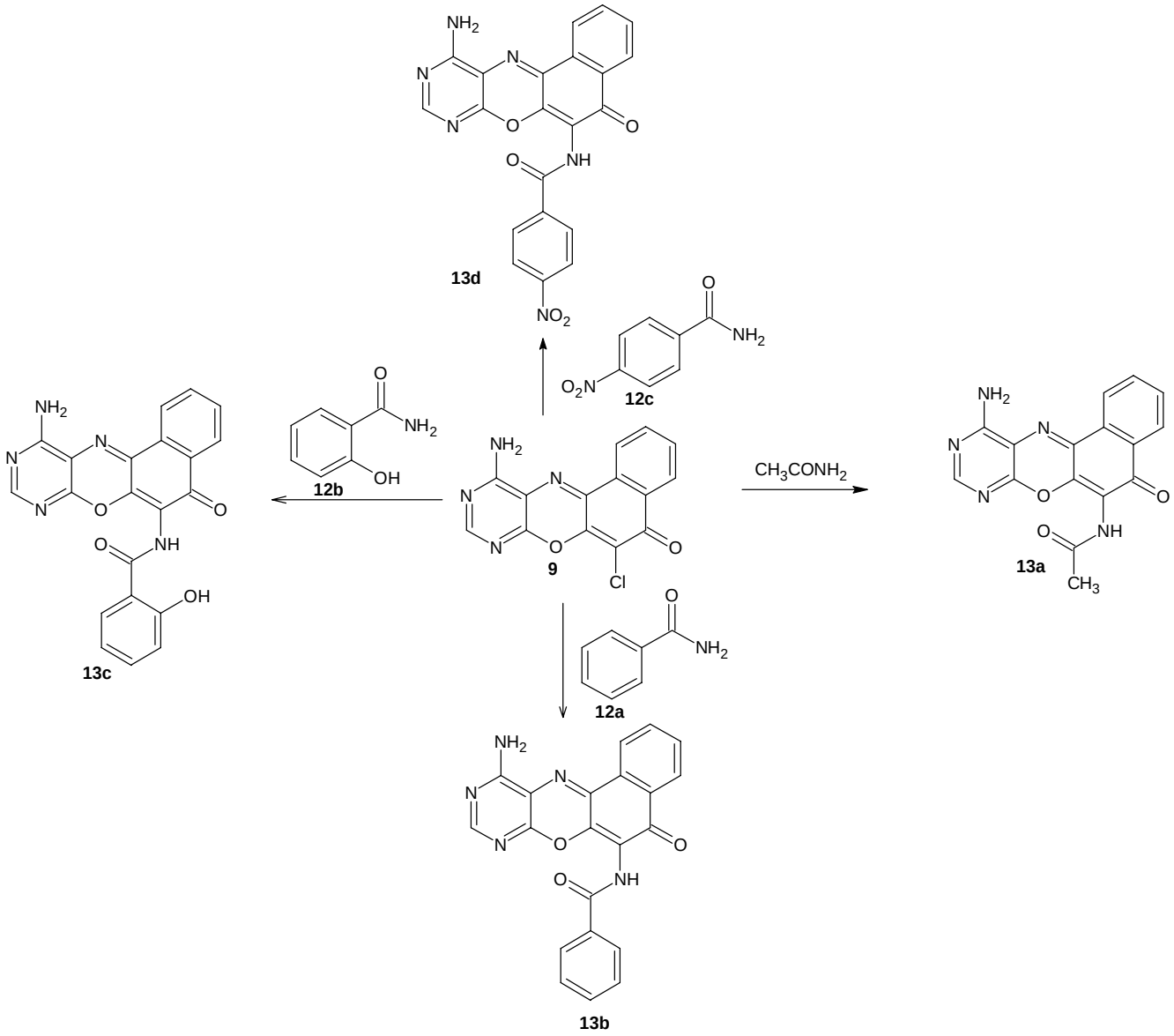
Scheme-I: Synthesis of 11-amino-6-chloro-8,10-diazabenzo[a]phenoxazin-5-one



Scheme-II: Preparation of amides

The acids include benzoic acid, 2-hydroxybenzoic acid and 4-nitrobenzoic acid to generate benzamide, 2-hydroxybenzamide and 4-nitrobenzamide, respectively. The acetamide was sourced commercially.





Scheme-III: Synthesis of 11-amino-6-amido-8,10-diazabenzo[a]phenoxazin-5-ones

Conclusion

The synthesis of 11-amino-6-chloro-8,10-diazabenzo[a]-phenoxazinone (**9**) and its transformation to the various substituted amide derivatives (**13a-d**) *via* Buchwald-Hartwig tandem amidation protocol has been achieved successfully. The structural assignments were supported by ultraviolet/visible, Fourier transform infrared, ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis.

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