
Airo
NATIONAL JOURNAL
ISSN : 23213914
Volume : VIII
A Multidisciplinary Indexed National Research Journal

An assessment of Benzimidazole derivatives and their Biological evaluation, Synthesis Process & Characterization

Srikantha Reddy Mettu
Research Scholar Mewar University
Dr. Pannala Padmaja
Research Supervisor Mewar University Mewar Rajasthan, India

ABSTRACT

Benzimidazole subordinates assume imperative part in therapeutic field with such a large number of Pharmacological exercises, for example, antimicrobial, antiviral, antidiabetic and anticancer movement. The power of these clinically helpful medications in treatment of microbial diseases and different exercises supported the advancement of some more strong and huge mixes. Benzimidazoles are astoundingly compelling mixes, broad biochemical and pharmacological reviews have affirmed that these atoms are powerful against different strains of microorganisms. This audit is condensed to think about the science of various subsidiaries of substituted benzimidazoles alongside their pharmacological exercises. Benzimidazoles and its subordinates speak to a standout amongst the most naturally dynamic class of compounds, having a wide range of exercises and these are all around archived in writing. They indicate particular neuropeptides YY1receptor antagonists, powerful inhibitors of TIE-2 and VEGFER-2 tyrosine kinase receptors, antitumor agents, gamma-amino butyric corrosive (GABA) agonists, and 5-HT3 antagonists.[1] Substituted benzimidazole subsidiaries have discovered business application in veterinarian drug as anthelmintic operators and in different human helpful territories, for example, treatment of ulcers and antihistaminic.

INTRODUCTION

The most prominent methodologies for their amalgamation use N-alkylation of an unsubstituted benzimidazoles.[2] Ammonium salts are cheap, monetarily accessible reagents for couple of natural change responses, for example, halogenation of fragrant compounds and combination of 3, 4-dihydropyrimidine-2(1H)- ones.[3] However, there are no reports of the utilization of ammonium salts as impetuses

for the union of benzimidazoles. In continuation, on the blend of Heterocycles [4] and on the advancement of manufactured methodologies,[5] we thus report an effortless technique for the union of benzimidazoles by the buildup of 1, 2-phenylenediamine with carbonyl compounds, within the sight of ammonium salts in great yields. Tension is a mental and physiological state portrayed by intellectual, substantial, emotional, and behavioral parts. These segments join to make an offensive feeling that is ordinarily connected with uneasiness, dread or stress. Nervousness is a summed up state of mind or condition that happens without an identifiable activating jolt. Thusly, it is recognized from dread, which happens within the sight of a watched risk. Furthermore, dread is identified with the particular practices of escape and shirking, though, tension is the aftereffect of dangers that are seen to be wild or unavoidable. A few reports express that benzimidazoles have hostile to uneasiness activity. [6] This perception incited us to assess the integrated benzimidazole subsidiaries for against tension movement

MATERIALS AND METHODS

Every one of the chemicals and reagents utilized were of expository review and were secured from NICE Chemicals. It is realized that the response of o-Phenylenediamine (OPDA) with carbonyl compounds, under solid acidic conditions, gives benzimidazoles, while, OPDA within the sight of β-ketoesters under unbiased reflux conditions, gives benzodiazepin-2-ones, with the disposal of water and liquor. Under acidic conditions, at first it frames ethyl β-2-amino aniline crotonate at room temperature and after warming it gives 2-methyl-1H-benzo[d] imidazole rather than benzodiazepin-2-ones, with the end of ethyl acetic acid derivation. Subsequently, we have made an endeavor to respond OPDA with carbonyl compounds and b-ketoesters, with various ammonium salts to see the achievability of the arrangement of compounds. To choose great response conditions, we initially analyzed the model response of 1, 2-phenylenediamine (1 mol) with benzaldehyde (1 mol) within the sight of NH4 Br (1 mol), under dissolvable free conditions, at room temperature. The response was checked by thin-layer chromatography (TLC, fluent Hexane/ethyl acetic acid derivation 30/70) and 2-phenyl-1H-benzo[d] imidazole acquired in 20% yield. Correspondingly, the response was directed in various solvents, for example, CH3CN, MeOH, CHCl3, ether, and DMF;

CHCl3 was observed to be the most reasonable dissolvable that gave benzimidazole with 40% yield. Next, we completed a similar response with various ammonium salts, for example, NH4F, NH4Cl, NH4NO3, (NH4)2CO3, and (NH4)2SO4 within the sight of CHCl3, at room temperature; among these, NH4Cl (4 mol) gave 2-phenyl-1H-benzo[d]imidazole with 94% yield in 4 hours [Figure 1, Table 1]. The outcomes, arranged in Table 2, show the development of benzimidazoles.

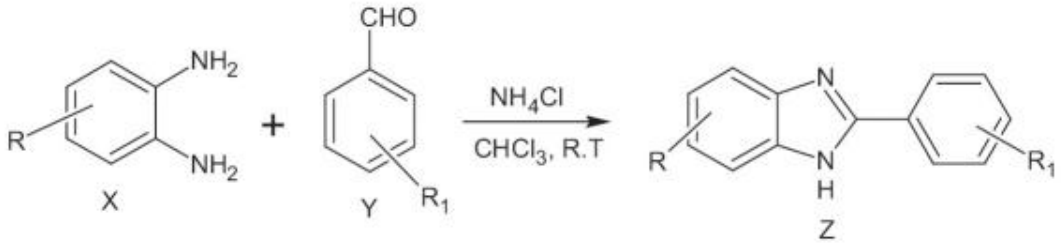


Figure 1: Ammonium halide catalyzed synthesis of 2-arylbenzimidazoles

Table 1: Optimization of reaction conditions for the synthesis of 2-phenyl benzimidazole by the condensation of OPDA, with benzaldehyde, using various ammonium salts at room temperature in $CHCl_3$

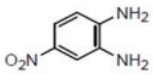
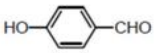
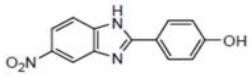
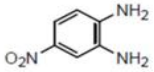
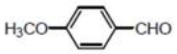
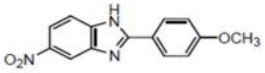
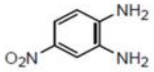
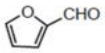
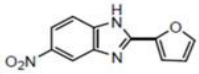
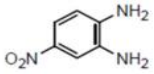
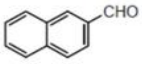
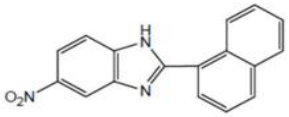
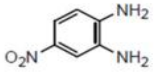
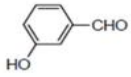
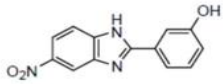
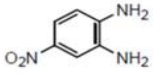
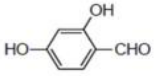
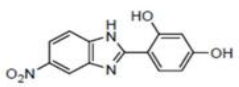
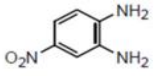
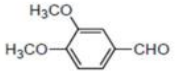
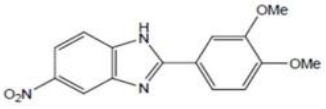
NH_4X[a]	Time (hours)	Yield (%)[b]
NH_4Br	4	86
NH_4Cl	4	92
NH_4F	5	72
$(NH_4)_2SO_4$	12	78
$(NH_4)_2CO_3$		82

[a]Reaction carried out with 4 mol of NH_4X
[b]Isolated and unoptimized yields

The blended compounds were examined by NMR, Mass, and IR spectroscopy. 1H NMR spectra were recorded on a Varian Gemini 200-and 300-MHz instrument in CDCl3 and DMSO-d6 utilizing Tetramethylsilane (TMS) as an inner standard. The mass spectra were measured on a Liquid Chromatography/Mass Spectrometry (LCMS) Agilent mass spectrometer. The IR spectra were recorded on a Nicolet 740 Fourier change infrared (FTIR) spectrometer. The liquefying focuses were

measured utilizing a Buchi-510 contraption and were uncorrected [7].

Table 2: Synthesis of benzimidazole derivatives

p				8	88
q				8	87
r				8	84
s				8	82
t				8	87
u				8	87
v				8	86

Typical Experimental Procedure for the Synthesis of Benzimidazoles

Benzaldehyde (Y, 1 mmol) was added to a mixed arrangement of 1,2-phenylenediamine (X, 1 mmol) and NH4Cl (4 mmol) in CHCl3 (5 ml) for five minutes at room temperature. Blending was proceeded for four hours. After culmination of the response (TLC, eluent Hexane/ethyl acetic acid derivation 30/70)[8], the dissolvable was expelled under lessened weight and separated with ethyl acetic acid derivation (20 ml); the natural layer was washed with water (10 ml). Layers were isolated and the natural layer was dried over sodium sulfate. The dissolvable was expelled under diminished weight and the unrefined item was subjected to section chromatography utilizing oil ether = EtOAc (9:1), which gave 2-phenyl-1H-benzo[d] imidazole (ZA) as a strong in 94% yield[9].

Spectral Data

2-phenyl-1H-benzimidazole:

Solid; Molecular formula: $C_{13}H_{10}N_2$, Yield-94%, m.p-296 °c;^{1}H NMR: δ 6.06 (bs, 1H, NH), 6.82 (d, 2H, aromatic), 6.98 (d,2H, aromatic), 7.06 (t,1H, aromatic),7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic), IR (KBr): 3426(-NH), 3042(Ar-CH), 1742, 1631(-C = N) cm^{-1}; Mass (LCMS): *m/z* 195 (M^+ + H).

4-(1H-benzimidazol-2-yl) phenol:

Solid; Molecular formula:$C_{13}H_{10}N_2O$, Yield - 78%, m.p-271 °c; ^{1}H NMR: δ 6.06 (bs, 1H, NH), 6.82 (d, 2H, aromatic), 6.98 (d,2H, aromatic), 7.21 (d,2H, aromatic),7.52 (d, 2H, aromatic), IR (KBr): 3379(-NH), 3211(-OH), 3078(-Ar-CH), 1461(C = N) cm-1; Mass (LCMS): *m/z* 211 (M^+ + H)[10].

6-nitro-2-phenyl-1H-benzimidazole:

Solid; Molecular formula:$C_{13}H_9N_3O_2$, Yield -82%, m.p-208 °c; ^{1}H NMR: δ 6.08 (bs, 1H, NH), 6.90 (d, 2H, aromatic), 6.96 (d,2H, aromatic), 7.05 (t,1H, aromatic), 7.54 (d,1H, aromatic),8.12 (d, 1H, aromatic), 8.44 (s, 1H, aromatic), IR (KBr): 3211(-NH), 2984(Ar-CH), 1552(-NO_2), 1529 (-C=N) cm^{-1}; Mass (LCMS): *m/z* 240 (M^+ +H).

2-(4-methoxyphenyl)-1H-benzimidazole:

Solid; Molecular formula:$C_{14}H_{12}N_2O$, Yield -85%, m.p-285 °c;^{1}H NMR: δ 3.70 (d,3H, OCH_3), 6.12 (bs, 1H, NH), 6.94 (d, 2H, aromatic), 6.98(d,2H, aromatic), 7.20 (d,2H, aromatic), 7.58 (d,2H, aromatic), IR (KBr): 3294(-NH), 3103(Ar-CH), 1184 (-OCH_3), 1588(-C=N) cm-1; Mass (LCMS): *m/z* 225 (M^+ +H).

2-(4-methylphenyl)-1H-benzimidazole:

Solid; Molecular formula:$C_{13}H_{12}N_2$, Yield - 88%, m.p-278 °c; ^{1}H NMR: δ 2.54 (d, 3H, CH_3),6.06 (bs, 1H, NH), 6.84 (d, 2H, aromatic), 6.96 (d,2H, aromatic), 7.18 (d,2H, aromatic),7.58 (d, 2H, aromatic), IR (KBr): 3346(-NH), 3024(Ar-CH), 2923(-CH_3), 1575(-C=N) cm-1; Mass (LCMS): *m/z* 209 (M^+ +H)[11].

4-(6-nitro-1H-benzimidazol-2-yl) phenol:

Solid; Molecular formula:$C_{13}H_9N_3O_3$, Yield -76%, m.p-237 °c;^{1}H NMR: δ 6.08 (bs, 1H, NH), 6.74 (d, 2H, aromatic), 6.84 (d, 2H, aromatic), 7.45 (d,1H, aromatic), 8.02 (d,1H, aromatic),8.32 (s, 1H, aromatic), IR (KBr): 3737(-OH),3432(-NH), 3103(Ar-CH), 1562(C=N), 1532(-NO_2) cm-1; Mass (LCMS): *m/z* 256 (M^+ +H).

2-(4-methylphenyl)-6-nitro-1H-benzimidazole:

Solid; Molecular formula:$C_{14}H_{14}N_3O_2$, Yield -86%, m.p-223 °c; ^{1}H NMR: δ 2.56 (d, 3H, CH_3),6.10 (bs, 1H, NH), 6.80 (d, 2H, aromatic), 6.86 (d,2H, aromatic), 7.54 (d,1H, aromatic),8.08 (d, 2H, aromatic), 8.44 (s, 1H, aromatic), IR (KBr): 3402(-NH), 3054(Ar-CH), 1534(-C=N), 1524(-NO_2) cm-1; Mass (LCMS): *m/z* 254 (M^+ +H).

4-(6-methyl-1H-benzimidazol-2-yl) phenol:

Solid; Molecular formula:$C_{14}H_{12}N_2O$, Yield -82%, m.p-245 °c;^{1}H NMR: δ 2.56 (d, 3H, CH_3), 6.48 (bs, 1H, NH), 6.78 (d, 2H, aromatic), 6.92 (d,2H, aromatic), 7.48 (d,1H, aromatic), 8.10 (d,1H, aromatic), 8.44 (s,1H, aromatic), IR (KBr): 3455(-OH), 3274(-NH), 3212(Ar-CH), 2898(-CH_3), 1534(-C=N) cm-1; Mass (LCMS): *m/z* 225 (M^+ +H).

Pharmacology

Wistar rats weighing 200 ± 25 g, of either sex, were secured no less than two weeks before the review. The creatures were housed in polycarbated confines under states of steady temperature (22 ± 2 °c) and stickiness, under a 12-hour light/dull calendar, the creatures were enabled free access to a standard eating regimen and water, so they could adapt to the new condition [12].

Intense oral poisonous quality reviews

The point of this review is to decide the deadly measurements. In this review the testing medication was regulated in a solitary measurement, utilizing the oral course. The dosage was expanded in an evaluated way. LD50 in the intense lethality test was seen at the measurements of 400 mg/kg-bw. In this manner, one-tenth of the previous measurement (200 mg/kg-bw) was chosen for the review, that is, 20 mg/kg-bw. This 20 mg/kg-bw testing measurement did not have any effect on the typical velocity of the creature, which was tried by controlling a similar dosage to the creatures, utilizing the oral course [13]. The locomotors movement was evaluated in a lacto photometer.

Hostile to uneasiness action

In this action, the hoisted in addition to labyrinth model was utilized. For this model, Wistar rats were separated into 10 gatherings of six creatures each. Gather I (control) creatures were regulated the

vehicle, Group-II, Group-III, Group-IV, Group-V, Group-VI, Group-VII, Group-VIII, and Group-IX creatures were directed the benzimidazole subsidiaries of ZA – ZH, individually, with a measurements of 20 mg/kg-bw (p.o), and Group-X was managed diazepam 2 mg/kg-bw (p.o), for 1 day if there should be an occurrence of intense review and for 10 days in the event of constant review[14]. The quantity of sections and time spent in the open and shut arms of the lifted in addition to labyrinth, utilizing rats, was seen in intense and endless reviews for 1day and 10 days, separately. Diazepam was utilized as a source of perspective standard. The examination was directed in a sound constricted room. In an intense review, the creatures of all gatherings were treated with the separate medications 30 minutes before the analysis. In an unending review, creatures of all gatherings were treated with the particular medications for 10 days, and on the tenth day, treatment was given 30 minutes preceding the analysis. In both intense and ceaseless reviews, each rodent was set in the focal point of the labyrinth confronting one of the encased arms, and amid a ten-minute session the accompanying parameters were noted; Number of sections away from any detectable hindrance arm, number of passages into the shut arm, time spent in the open arm, time spent in the shut arm, and aggregate number of passages beyond any confining influence and shut arms. [15]

Measurable Analysis

The qualities were communicated as mean ± SEM for six creatures. The outcomes were subjected to measurable investigation by utilizing one-way ANOVA taken after by Tukey-Kramer test, to figure the critical contrast, assuming any, among the gatherings. $P < 0.05$ was considered as huge.

RESULTS

The compounds (ZA – ZH) were gotten by the response amongst aldehyde and o-phenylediamine within the sight of ammonium salts as indicated by Figure 1. The integrated compounds were affirmed by thin layer chromatography (TLC), Melting Point (mp), IR, 1H NMR, and mass spectroscopy (MS) ghostly investigation. The yields and liquefying focuses for all the incorporated compounds are recorded in Table 2. The titled compounds were affirmed by IR unearthly information demonstrating trademark groups at 1384 – 3200 cm-1, showing the nearness of –NO2 and –OH extending; and sharp groups,

running between 1680 – 1750 cm-1, demonstrating the nearness of C = N. Compounds ZA – ZH were affirmed by extending at 3500 cm-1, because of the nearness of –NH. Compounds ZA – ZH were affirmed by 1 H NMR phantom examination. The NMR proton crest at 6.00 – 6.18 ppm uncovered the nearness of –NH. Assist appearance of the sub-atomic particle crest at 225 (m + 1) and 209 (m + 1) affirmed the structure of ZD and ZE.

Table 3: Effect of synthetic preparation on number of entries and time spent in elevated plus maze in acute study

Treatment group	Open arm entries	Closed arm entries	Total entries	Time spent in open arm	Time spent in closed arm
Control	2.5 ± 0.4282	2.16 ± 0.3073	4.66 ± 0.6667	16.83 ± 1.352	583.16 ± 1.352
Z_A	3.83 ± 0.3070	3.66 ± 0.4216	7.5 ± 0.7188	23 ± 1.673	577 ± 1.673
Z_B	4.50 ± 0.5627	4.33 ± 0.7149*	8.83 ± 1.249*	35.5 ± 1.310*	564.5 ± 1.310*
Z_C	4.16 ± 0.4773	3.83 ± 0.4773	8 ± 0.8563	19.83 ± 1.249	580.16 ± 1.249
Z_D	2.66 ± 0.3333	3 ± 0.2582	5.66 ± 0.4216	17.83 ± 1.579	582.16 ± 1.579
Z_E	5.16 ± 0.4773*	4.83 ± 0.3073**	10 ± 0.6831**	92.16 ± 6.085***	507.83 ± 6.085***
Z_F	5 ± 0.3651*	5 ± 0.4475***	10 ± 0.6831**	101.66 ± 3.432***	498.33 ± 3.432***
Z_G	5.16 ± 0.6009*	5 ± 0.3651***	10.16 ± 0.9098**	104.33 ± 3.658***	495.66 ± 3.658***
Z_H	5.66 ± 0.7601**	5.66 ± 0.3333***	11.33 ± 1.685***	115.33 ± 4.835***	484.66 ± 4.835***
Std (Dizepam)	6.5 ± 0.4282***	6.83 ± 0.4773***	13.33 ± 0.8028***	134.16 ± 4.430***	465.83 ± 4.430***

DISCUSSION

A few analysts announced a synthesis of benzimidazole subordinates, yet in our present review we integrated the benzimidazole subsidiaries by utilizing ammonium salts as impetuses, which were reasonable and diminished the response time, with great yields. This technique could be effectively polished in research centers inside the stipulated time.

In the assessment of against tension action, the test display utilized as a part of our review was a hoisted in addition to labyrinth. This depended on the suspicion that new, non-defensive, and splendidly lit ecological anxiety incited hindrance of typical conduct. This typical behavioral

hindrance was additionally increased within the sight of dread or a tension like state.[24] The raised in addition to labyrinth test was an entrenched creature demonstrate for testing anxiolytic drugs. A known anxiolytic drug, diazepam, was utilized as the standard,

which is one of the very much perceived anxiolytic drugs. In this model, the progressions that happened because of tension were, diminished time spent in the open arm, expanded time spent in the shut arm, and diminished number of sections between the arms, than that which was seen in the control creatures.

CONCLUSION

The present review portrays a straightforward, modest, and simple strategy for synthesis of benzimidazole subordinates in a stipulated time, without utilizing any radical conditions. The yield of all benzimidazole subordinates were observed to be in the scope of 75 – 94%. The virtue of the compounds were found out by a softening point and TLC. The doled out structure was additionally settled by IR,1 HNMR, and MS unearthly reviews.

The intense and perpetual reviews for against uneasiness movement of the combined compounds were screened utilizing hoisted in addition to labyrinth technique in Wistar rats. Diazepam was utilized as the reference drug. In the arranged benzimidazole subordinates, it appeared that the compounds ZB[4-(1H-benzimidazol-2-yl) phenol], ZE[2-(4-methylphenyl)- 1H-benzimidazole], ZF[4-(6-nitro-1H-benzimidazol-2-yl) phenol], ZG[2-(4-methylphenyl)- 6-nitro-1H-benzimidazole], and ZH[4-(6-methyl-1H-benzimidazol-2-yl) phenol] indicated strong action when contrasted with the standard drug diazepam. The compound ZH[4-(6-methyl-1H-benzimidazol-2-yl) phenol] displayed the most elevated hostile to uneasiness action when contrasted with the other arranged benzimidazole compounds.

REFERENCES

1. Babu KS, China Raju B, Srinivas PV, Rao AS, Kumar SP, Rao JM. A simple, effective, and highly selective cleavage of 3-methylbut-2-enyl (prenyl) ethers using *p*-toluenesulfonic acid. Chem Lett. 2003;32:704.
2. Babu KS, China Raju B, Srinivas PV, Rao JM. Highly efficient and chemo selective cleavage of prenyl ethers using ZrCl4-NaBH4. Tetrahedron Lett. 2003;44:2525.
3. China Raju B, Neelakantan P, Bhalerao UT. Quinone methide initiated cyclization reaction: Synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines. Tetrahedron Lett. 2004;45:7487.
4. Czarny A, Wilson WD, Boykin DW. Synthesis of mono cationic and dicationic analogs of Hoechst 33258. J Heterocycl Chem. 1996;33:1393.
5. Falco J, Pique M, Gonzalez M, Buira I, Mendez E, Terencio J, et al.

Synthesis, pharmacology, and molecular modeling of N-substituted 2-phenyl-indoles and benzimidazoles as potent GABA(A) agonists. Eur J Med Chem.2006;41:985–90. [PubMed]

6. Gangadasu B, China Raju B, Rao VJ. A simple and convenient preparation of 2-chloro-5-methylpyridine-3-carbaldehydeimines. Heterocycl Comm. 2002;8:243.
7. Gangadasu B, Narender P, Ramesh C, China Raju B, Rao VJ. Facile and selective synthesis of chloronicotin aldehydes by the vilmeier reaction. Tetrahedron. 2006;62:8398.
8. Grimmet MR, Katritzky AR, Rees CW. Hetero cyclic chemistry. Vol. 5. Oxford, UK: 1984. p. 457.
9. Hasegawa M, Nishigaki N, Washio Y, Kano K, Harris PA, Sato H, et al. Discovery of novel benzimidazoles as potent inhibitors of TIE-2 and VEGFR-2 tyrosine kinase receptors. J Med Chem. 2007;50:4453–70. [PubMed]
10. Hranjec M, Kralj M, Piantanida I, Sedic M, Suman L, Pavelic K, et al. Novel cyano- and amidino-substituted derivatives of styryl-2-benzimidazoles and benzimidazo[1,2-a]quinolines.Synthesis, photochemical synthesis, DNA binding, and antitumor evaluation, part 3. J Med Chem. 2007;50:5696–711. [PubMed]
11. Kim BH, Han R, Kim JS, Jun YM, Baik W, Lee BM. Simple and mild procedures for synthesis ofbenzimidazoles using heterogeneous catalyst systems. Heterocycles. 2004;62:41–54.
12. Latif N, Mishriky N, Assad FM, Meguid SB. b-Nitrostyrenes with *o*-Phenylenediamine: A new route of the synthesis of 2-substituted benzimida-zoles. Indian J Chem. 1982;21B:872.
13. Maryanoff BE. Potential anxiolytic agents.Pyrido[1, 2-a] benzimidazoles: A new structural class of ligands for the benzodiazepine binding site on GABA-A receptors. J Med Chem. 1995;38:16–20. [PubMed]
14. Narender P, Gangadasu B, Ramesh C, China Raju B, Rao VJ. Facile and selective synthesis of chloromethylpyridines and chloropyridines using diphosgene-triphosgene. Synth Commun. 2004;34:1097.
15. Phillips MA. The formation of 2-substituted benzimidazoles. J Chem Soc. 1928;JR9280002393:2393.
16. Spasov AA, Yozhitsa IN, Bugaeva LI, Anisimova VA. Rearrangement strategy for the syntheses of 2-amino anilines. Pharm Chem J. 1999;33:232–43.
17. Tidwell RR, Geratz JD, Dann O, Volz G, Zeh D, Loewe H. Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esteroproteases. J Med Chem. 1978;21:613–23. [PubMed]
18. Wu Z, Rea P, Wickam G. Tetrahedron Lett. 2000;41:9871-4, and the reference cited therein; Mazurov A.Bioorg Med Chem Lett. 2000;10:67–70.
19. Zarrinmayeh H, Nunes AM, Ornstein PL, Zimmerman DM, Arnold MB, Schober DA, et al. Synthesis and evaluation of a series of novel 2-[(4-chlorophenoxy)methyl]benzimidazol

es as selective neuropeptide Y Y1 receptor antagonists. J Med Chem. 1998;41:2709–19. [PubMed]