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Design, characterization and pharmacophoric evaluation of new series of N-substituted benzamides

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Abstract

The newer benzamides were designed by taking into consideration, the pharmacophoric distances of reported anticonvulsant agents. From this study and observation from literature regarding the importance of benzamide moiety novel N-substituted benzamides were synthesized. 4-amino-3,5dichlorobenzoylchloride was the main intermediate, was condensed with various amines which gave 4-amino-3, 5 dichloro-N-substituted benzamides. Amidation reaction of acid chloride and six different amines was carried out conventionally and also on six station parallel synthesizer which offered improvement in yield of final compounds in short period. The lead compounds were characterized by melting point, TLC, IR, and ^{1}H NMR studies. Further work leading to the evaluation of these compounds in various anticonvulsant models, to establish their efficacy as anticonvulsant agents is requested.

Key words: N-substituted benzamides, pharmacophoric evaluation, synthesis.

INTRODUCTION

Benzamides are reported to posses Antiemetic, Antipsychotic, Antiarrythmic Activity [1,2]. Various N- substituted derivatives of benzamides are reported to posses Anticonvulsant Activity [3-5]. In the present we work report the design of new series of N-substituted Benzamides by taking into consideration of the pharmacophoric distances of reported compounds. Six novel compounds were synthesized as part of the present work. 4-amino-3,5dichlorobenzoylchloride was the main intermediate was condensed with various amines gave 4-amino-3,5 dichloro-N-substituted benzamides. Amidation reaction of acid chloride and six different amines was also carried out on six station parallel synthesizer which offered improvement in yield of final compounds in short period.

RESULTS AND DISCUSSION

The two-point pharmacophore of reported compounds was generated using Molecular Operating Environment (MOE) software version 2005.06. The essential requirement for anticonvulsant activity was found to be presence of at least one aromatic ring and hydrogen bond donor/acceptor unit. The distances of hydrogen bond donor/acceptor to aromatic region for reported compounds were in the range of 3.46-6.84 A while the designed series was 3.47- 4.62 A^0. Designed series of N-substituted benzamides were synthesized by oxidative chlorination of p- amino benzoic acid (1) which gave 4-amino-3,5-dichorobenzoic acid (2). The acid halide (3) was obtained using phosphorus pentachloride, which was further condensed with various substituted amines yielded the desired series of N-substituted benzamides (4a-f). Amidation reaction of acid chloride and six different amines was also carried out on six station parallel synthesizer MINIBLOCK^{TM} XT. In the conventional synthesis, average yield of final substituted benzamides was 55-60% while in parallel synthesizer 75-80%. The time taken for completion was 10 min. Parallel synthesizer offered advantage of precise temperature control, efficient magnetic stirring, and easy reaction set up, and more synthesized compounds per unit time with improved yields of final product. Yields of last step were optimized by varying temperature condition and stirring. The homogenity of the compounds was monitored by thin layer chromatography (TLC) on silica-G (Merck) coated glass plates, visualized by iodine vapour. The compounds were characterized by ^{1}H nuclear magnetic resonance, FT-infrared spectroscopy in which it complies with normal values.

In the present work six derivatives of 4-amino-3,5 dichloro-N-substituted benzamides were synthesized by convential and parallel synthesizer. Fig 1.

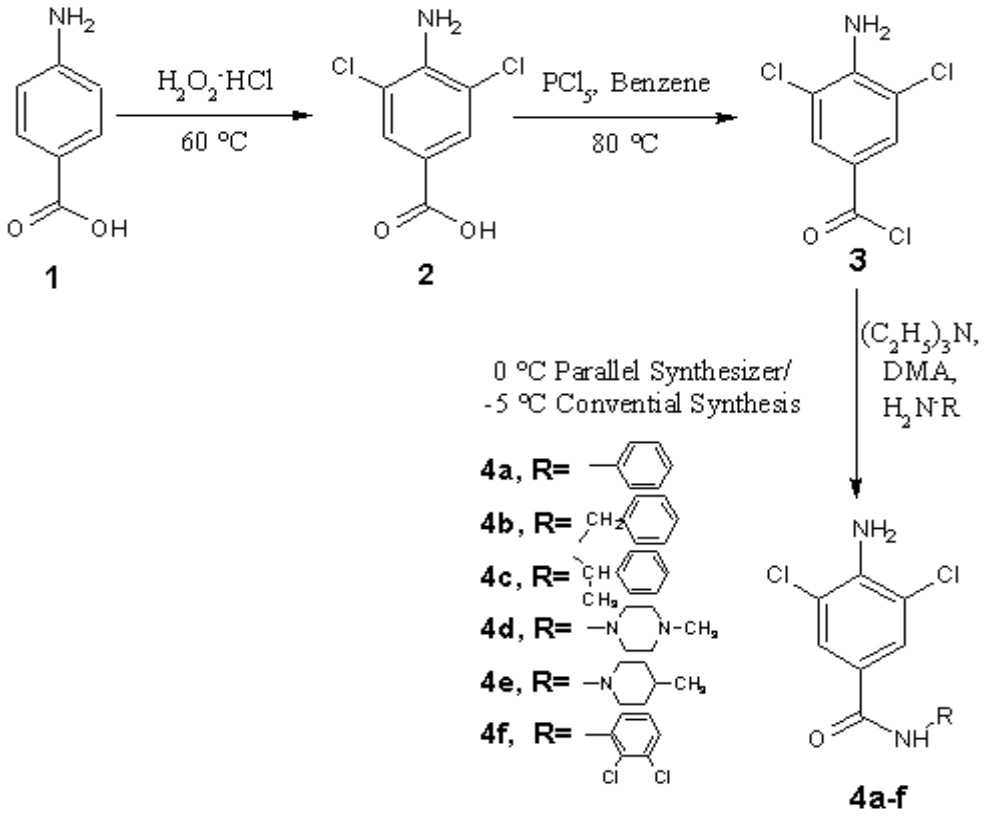

Fig 1: Scheme for Synthesis: Synthetic protocol of N-substituted benzamides

Experimental

Pharmacophore development

Pharmacophore study was carried out by Molecular Operating Environment (MOE; version 2005.06, Canada) working on Pentium IV Windows workstation. A two-point pharmacophore was designed using a training set of antiepileptic drugs such as phenytoin, carbamazepine, lamotrigine, rufinamide and remacemide. The important structural features essential for anticonvulsant activity were identified. This pharmacophore was used to design the newer molecules by restricting the distance (3.46-6.84 A^0) from Hydrogen bond acceptor or donor to aromatic center. The test compounds showed a good map on designed pharmacophore (r^2 = 0.942). There were presence of at least one phenyl ring and H-bond acceptor / donor group (H.A/D). (Fig 2).

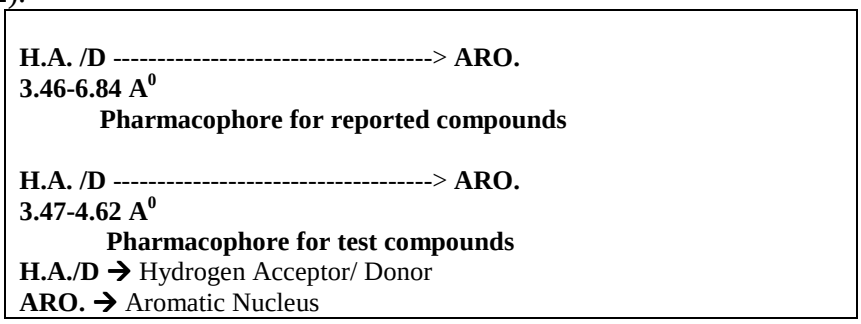

Fig 2: Pharmacophore studies of compounds

Synthesis of designed series

Melting points were determined in open capillary tubes on a Thermonik melting point apparatus and are uncorrected. Wherever required solvents were removed *in vacuo* on 'BUCHI' rotaevaporator. Infrared (IR) spectra were recorded for the compounds on Jasco FT/IR 5300 (KBr). The ^{1}H-NMR (300.0 MHz) spectra were recorded on Varian VX-300 (Fourier Transform) instrument. In proton nuclear magnetic resonance spectroscopy all exchangeable protons were confirmed by addition of D_2O. Chemical shifts are reported in ppm (δ) using tetra-methyl silane (TMS) as internal standard. All solvents & reagents used were of laboratory grade. All the solvents were distilled prior to use. 4-amino-3,5-dichlorobenzoic acid **(2)** was synthesized from p-amino benzoic acid **(1)** according to the earlier reported methods [6].

4-amino-3,5-dichlorobenzoic acid: Yield: 62.22% m.p. 290^{0}C (lit. 291^{0}C)

4-amino-3,5 dichlorobenzoyl chloride **(3)** was synthesized from 4-amino-3,5 dichlorobenzoic acid **(2)** according to the earlier reported methods [7].

The crude Compound **(3)** was taken up for further synthesis.

Condensation of amines with 4-amino-3,5 dichlorobenzoylchloride[8]: (4a-4f)

Compound (3) was dissolved in dimethylacetamide (DMA) condensed with six different amines for preparation of substituted benzamides.

Synthesis of 4-amino-3,5-dichloro-N-phenyl benzamide (4a)

In a 50 ml RBF fitted with anhydrous calcium chloride guard tube the mixture of 0.37g (0.004 M) aniline in 0.44g (0.004 M) triethylamine and 1.44g DMA was stirred at 0ºC. To this mixture, 1g (0.004 M) of Compound (3) in 2.2 ml of DMA was added dropwise. Reaction was continued for 30 mins., cold water was added to the reaction mixture and further stirred for 30 min. Separated solid was filtered and recrystalized from methanol:water mixture. M.P.: 160 ºC, Yield: 0.8g (61.53 %).

Synthesis of 4-amino-3,5-dichloro-N-benzyl benzamide (4b)
In a 50 ml RBF fitted with anhydrous calcium chloride guard tube the mixture of 0.42g (0.004 M) benzyl amine in 0.44g (0.004 M) triethylamine and 1.44g DMA was stirred at 0ºC. To this mixture, 1g (0.004 M) of Compound (3) in 2.2 ml of DMA was added dropwise. Reaction was continued for 30 mins, cold water was added to the reaction mixture and further stirred for 30 min. Separated solid was filtered and recrystalized from methanol-water mixture. M.P.: 120 ºC, Yield: 0.9g (67.85 %).

Synthesis of 4-amino-3,5-dichloro-N-phenylethyl benzamide (4c)
In a 50 ml RBF fitted with anhydrous calcium chloride guard tube the mixture of 0.53g (0.004 M) phenylethylamine in 0.44g (0.004 M) triethylamine and 1.44g DMA was stirred at. 0ºC. To this mixture, 1g (0.004 M) of Compound (3) in 2.2 ml of DMA was added dropwise. Reaction was continued for 30 mins, cold water was added to the reaction mixture and further stirred for 30 min Separated solid was filtered and recrystalized from methanol-water mixture. M.P.: 200 ºC, Yield: 0.9g (64.66 %).

Synthesis of 4-amino-3,5-dichloro-N-(4-methylpiperizine) benzamide (4d)
In a 50 ml RBF fitted with anhydrous calcium chloride guard tube the mixture of 0.44g (0.004 M) N-methyl piperazine in 0.44g (0.004 M) triethylamine and 1.44g DMA was stirred at 0ºC. To this mixture, 1g (0.004 M) of Compound (3) in 2.2 ml of DMA was added dropwise. Reaction was continued for 30 mins, cold water was added to the reaction mixture and further stirred for 30 min. Separated solid was filtered and recrystalized from methanol-water mixture. M.P.: 128 ºC, Yield: 0.7g (53.84 %).

Synthesis of 4-amino-3,5-dichloro-N-(4-methylpiperidine) benzamide (4e)
In a 50 ml RBF fitted with anhydrous calcium chloride guard tube the mixture of 0.39g (0.004 M) 4-methyl piperidine in 0.44 g (0.004 M) triethylamine and 1.44 g DMA was stirred at 0ºC. To this mixture, 1g (0.004 M) of Compound (3) in 2.2 ml of DMA was added dropwise. Reaction was continued for 30 mins, cold water was added to the reaction mixture and further stirred for 30 min.Reaction mixture was extracted using ethyl acetate and solvent was removed on rotary evaporator. B.P.: 55 ºC, Yield: 0.72g (51.79 %).

Synthesis of 4-amino-3,5-dichloro-N-(2,3 dichloro phenyl) benzamide (4f)
In a 50 ml RBF fitted with anhydrous calcium chloride guard tube the mixture of 0.6g (0.004 M) benzyl amine in 0.44g (0.004 M) triethylamine and 1.44g DMA was stirred at 0ºC.To this mixture, 1g (0.004 M) of Compound II in 2.2 ml of DMA was added dropwise. Reaction was continued for 30 mins, cold water was added to the reaction mixture and further stirred for 30 min. Separated solid was filtered and recrystalized from methanolwater mixture. M.P.: 220ºC, Yield: 0.9g (68.75 %).

Amidation reaction of acid chloride and six different amines was also carried out on six station parallel synthesizer MINIBLOCK ™ XT (Fig 3). Yields of last step were optimized by varying temperature condition and stirring. Comparative values for conventional and parallel synthesizer are given in Table 1.

Fig 3. MINIBLOCK™ XT Parallel Synthesizer

Table 1: Yields of the synthesized substituted benzamides

SR. NO.	Yield (%)		Temperature (^{0}C)		Speed (rpm)
	Conventional Synthesis	Parallel Synthesis	Conventional synthesis	Parallel synthesis	
III	61.53	93.84	-5 ^{0}C	0 ^{0}C	100
IV	67.85	87.32	-5 ^{0}C	0 ^{0}C	100
V	64.66	85.33	-5 ^{0}C	0 ^{0}C	100
VI	53.84	61.60	-5 ^{0}C	0 ^{0}C	100
VII	51.79	56.20	-5 ^{0}C	0 ^{0}C	100
VIII	68.75	71.42	-5 ^{0}C	0 ^{0}C	100

Table 3: Characterization of compounds 4a-4f

Compound	M.P(^{0}C)	Spectral Data Units: I.R. in cm^{-1}, ^{1}H NMR in ppm at 300 MHz.
4a	160 ^{0}C	**I.R (KBr):** 3495 (N-H, amine), 3425 (N-H, amide), 3072 (C-H), 1612 (C=O), 704 (C-Cl). **1H-NMR ($CDCl_3$):** 7.62 (m, 5H, Ar), 7.72 (m, 3H, Ar), 4.8 (s, 2H, 2 N-H).
4b	120 ^{0}C	**I.R (KBr):** 3369 (N-H, amine), 3290 (N-H, amide), 3028 (C-H), 1612 (C=O), 798 (C-Cl). **1H-NMR ($CDCl_3$):** 7.4 (m, 5H, Ar), 7.65 (s, 2H, Ar), 6.2 (s, 1H, 1 N-H), 4.8 (s, 2H, 2 N-H), 4.6 (d, 2H, -CH_2).
4c	200 ^{0}C	**I.R (KBr):** 3476 (N-H, amine), 3362 (N-H, amide), 3072 (C-H), 1620 (C=O), 794 (C-Cl). **1H-NMR ($CDCl_3$):** 7.4 (m, 5H, Ar), 7.6(s, 2H, Ar), 6.2 (s, 1H, 1 N-H), 5.4 (m, 1H, -CH_3).
4d	128 ^{0}C	**I.R (KBr):** 3404 (N-H, amine), 2972 (C-H), 1602 (C=O), 1458 (C-H), 802 (C-Cl). **1H-NMR (DMSO-d_6):** 5.8 (s, 2H, N-H), 7.2 (s, 2H, Ar), 3.5 (m, 4H, Aliphatic), 2.8 (m, 4H, Aliphatic), 2.19 (s, 3H, -CH_3).
4e	55 ^{0}C	**I.R (KBr):** 3477 (N-H, amine), 3335 (N-H, amide), 3069 (C-H), 1614 (C=O), 798 (C-Cl). **1H-NMR ($CDCl_3$):** 4.8 (s, 2H, N-H), 7.29 (s, 2H, Ar), 1.65 (m, 4H, Aliphatic), 2.8-4.0 (m, 4H, Aliphatic), 0.95 (d, 3H, -CH_3), 1.2 (m, 1H, Aliphatic).
4f	220 ^{0}C	**I.R (KBr):** 3479 (N-H, amine), 3435 (N-H, amide), 2922 (C-H), 1618 (C=O), 777 (C-Cl). **1H-NMR ($CDCl_3$):** 4.8 (s, 2H, N-H), 7.75 (s, 2H, Ar), 8.48 (dd, 1H, Ar), 8.42 (dd, 1H, Ar), 7.27 (m, 2H, N-H).

CONCLUSION

Pharmacophore studies helped in the rational drug desined of new series of N-substituted benzamides (Figure **1**). Use of phosphorous pentachloride, instead of thionyl chloride in the synthesis of step (II) in Scheme **1** avoided the formation of polymer and improved the yields. Parallel synthesizer provides effective temperature control, stirring and more number of compounds per unit time. Anticonvulsant screening of newly synthesized compounds III-VIII will help in ascertaining the contribution of these novel structural features towards activity and will further help in refining the structural features required for anticonvulsant activity.

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