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Research Article

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Synthesis of analogues of trifenagrel using phase transfer catalyst tetrabutyl ammonium hydrogen sulphate (TBAHS)

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ABSTRACT

We report asynthesis of analogues of trifenagrel using selected substituted benzaldehydes namely 3-hydroxy benzaldehyde, 4-hydroxybenzaldehyde and vanillin. Condensation of aminoethoxy benzaldehydes with benzil and ammonium acetate using catalytic amount of tetrabutylammonium hydrogen sulphate (TBAHS) resulted in the desirable analogues of trifenagrel. Nine analogues were synthesized and characterized by their IR, ^{1}H NMR, Mass spectrums

Keywords: trifenagrel, 3-hydroxy benzaldehyde, 4-hydroxybenzaldehyde, vanillin, and tetrabutylammonium hydrogen sulphate (TBAHS)

INTRODUCTION

The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles[1] Imidazoles have received significant attention due to their synthesis, reactions and biochemical properties. Even today, research in imidazole chemistry continues undebated because compounds with imidazole moiety have immense biological and pharmaceutical importance. [2]

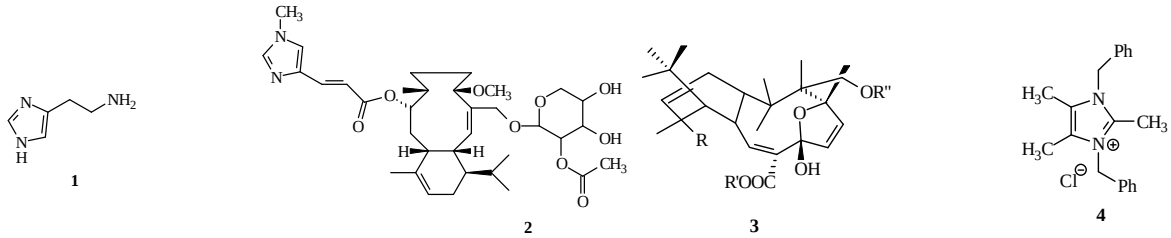


Figure-1

Part of the motivation for pursing libraries of imidazoles is their prevalence in naturally occurring and synthetic biologically active compounds. The well-known naturally occurring imidazole like histamine (**1**) is known to be responsible for allergic manifestations such as asthma and urticarial on its release in the body[3]. Eleutherobin (**2**) and sarcodictycin [4] (**3**) among numerous other marine and plant derived natural products[5] are known for microtubule stabilizing agent. Lepidiline A and B (**4**) which are highly substituted imidazoles were recently isolated from the root extract of *Lepidium meyenii* collected from the Andes Mountains of Peru [6] and are known to exhibit micromolar cytotoxicity against several human cell lines.

EXPERIMENTAL SECTION

3-(2-Bromoethoxy)-benzaldehyde (3):
In a 50 mL two necked RB flask, 3-hydroxybenzaldehyde (3.10 g, 25.4 mmol), 1,2-dibromoethane (19.0 g, 101 mmol) and methanol (25 mL) were taken and heated to reflux. Then with stirring, 6N NaOH (5 mL) was added in 1 mL portions with 30 min interval between additions. After 18 h of stirring at reflux, workup and obtain crude product as brown syrup which was chromatographed over silica gel (60-120 mesh) using hexane: ethyl acetate (8 : 2) as eluent to obtain titled compound **3** (3.2 g, 52%) as brownish liquid. IR (Neat): υ 3446, 1695, 1258 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.56 (t, 2H, $-CH_2$), 4.25 (t, 2H, $-CH_2$), 7.00-7.12 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.30-7.42 (m, 2H, Ar-H), 9.86 (s, 1H, -CHO). EI-MS : *m/z* = 229 $[M]^+$.

3-(2-Dimethylaminoethoxy)benzaldehyde (**5a**)**:**
In a 100 mL RB flask, 3-(2-bromoethoxy)-benzaldehyde (2 g, 2.18 mmol), 40% dimethylamine solution (5 mL, 40.8 mmol) and methanol (15 mL) were taken, arranged for stirring at room temperature for 6 h. After 6 h the methanol was removed compound **5a** (1.5 g, 88.8%) as pale yellow solid. Mp: 176-177 ^{0}C. IR (KBr) : υ2958, 2117, 1679, 1596, 1260, 1165, 800, 749 cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.85 (s, 6H, 2 × CH_3), 3.56 (t, 2H, $-CH_2$), 4.45 (t, 2H, $-CH_2$), 7.30-7.40 (m, 1H, Ar-H), 7.46-7.53 (m, 1H, Ar-H), 7.60-7.62 (m, 2H, Ar-H), 10.00 (s, 1H, -CHO). EI-MS : *m/z* =193 $[M]^+$.

3-(2-Piperidinoethoxy)benzaldehyde (5b):
In a 100 mL RB flask, 3-(2-bromoethoxy)benzaldehyde (3.0 g, 13.1mmol), piperidine (3.1 g, 36.4 mmol) and methanol (30 mL) were taken and refluxed with stirring. After 3 h of reflux and workupthe reaction mass,concentrated to obtain the titled compound **5b** (1.85 g, 64%) as brown syrup. IR (Neat):υ 3420, 2932, 1695, 1260 cm^{-1}. ^1H NMR ($CDCl_3$):δ 1.40-1.60 (m, 6H, 3 × $-CH_2$), 2.45 (t, 4H, 2 x $-CH_2$), 2.72 (t, 2H, $-CH_2$), 4.16 (t, 2H, $-CH_2$), 6.92-6.94 (m, 1H, Ar-H), 7.75-7.82 (m, 3H, Ar-H), 9.88 (s, 1H, -CHO). ESI-MS : *m/z* = 234 $[M+H]^+$.

3-(2-Morpholinoethoxy)-benzaldehyde (5c):
3-(2-bromoethoxy)-benzaldehyde (5 g, 21.8 mmol), morpholine (5.24 g, 60.2 mmol) and methanol (100 mL) to obtain the titled compound **5c** (3.15 g, 61.47%) as brown syrup. IR (Neat): υ3445, 1695, 1260 cm^{-1}. ^1H NMR ($CDCl_3$):δ2.53 (t, 4H, 2 x $-CH_2$), 2.76 (t, 2H, $-CH_2$), 3.65 (t, 4H, 2 x $-CH_2$), 4.46 (t, 2H, $-CH_2$), 7.12-7.16 (m, 1H, Ar-H), 7.23 (m, 1H, Ar-H), 7.40-7.42 (m, 2H, Ar-H), 9.93 (s, 1H, -CHO). ESI-MS : *m/z* = 236 $[M+H]^+$.

2-(3-[2-Dimethylaminoethoxy)phenyl]-4,5-diphenylimidazole (7a):
benzil (840 mg, 4.0 mmol), 3-(2-dimethylaminoethoxy) benzaldehyde (840 mg, 4.0 mmol), ammoniumacetate (108 mg, 14.0 mmol), catalyst TBAHS (30 mol%) were taken and heated at 120° C with stirring for 6 h. After completion of the reaction the reaction mixture was cooled to room temperature and diluted with acetone (20 mL). after workup obtain the titled compound **7a** (70 mg, 79.7%) as solid. Mp: 183-184 ^{0}C. IR (KBr): υ3423, 3057, 2926, 2815, 2762, 1594, 1461, 1233, 649 cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.36 (s, 6H, 2 × CH_3), 2.81 (t, 2H, $-CH_2$), 4.15 (t, 2H, $-CH_2$), 6.70-6.80 (m, 1H, Ar-H), 7.21-7.40 (m, 7H, Ar-H), 7.54-7.62 (m, 4H, Ar-H), 7.62-7.72 (m, 2H, Ar-H). ESI-MS : *m/z* = 384 $[M+H]^+$. Anal.cacld.for: $C_{25}H_{25}N_30$: C, 78.30; H, 6.57. Found: C, 78.38; H, 6.48.

2-(3-[2-(Piperidino)ethoxy)phenyl]-4,5-diphenylimidazole (7b):
7b also prepared using above process (180 mg, 62.8%) as brown solid. Mp: 143-144 ^{0}C. IR (Neat):υ 3423, 2925, 1026 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6):δ 1.45-1.53 (m, 2H, $-CH_2$), 1.65-1.70 (m, 4H, 2 x $-CH_2$), 2.60-2.72 (m, 2H, $-CH_2$), 2.90 (t, 2H, $-CH_2$), 4.26 (t, 2H, $-CH_2$), 6.75 (d, 2H, Ar-H), 7.16-7.30 (m, 5H, Ar-H), 7.50-7.56 (d, *J* = 6.89 Hz, 4H, Ar-H), 7.62-7.66 (m, 2H, Ar-H), 7.82 (m, 1H, Ar-H). ESI-MS : *m/z* = 424 $[M+H]^+$. Anal.cacld.for: $C_{28}H_{29}N_30$: C, 79.40; H, 6.89. Found: C, 79.50; H, 6.98.

2-(3-[2-(Morpholino)ethoxy)phenyl]-4,5-diphenylimidazole (7c):
Prepared following the procedure described for (**7a**) using benzil (840 mg, 4.0 mmol), 3-(2-morpholinoethoxy) benzaldehyde (102 mg, 4.2 mmol), ammoniumacetate (10.8 mg, 14 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound (580 mg, 63.68%) **(7c)** as pale brown solid. Mp: 215-217 ^{0}C. IR (Neat): υ3420, 1655, 1024 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.56 (t, 4H, 2 x $-CH_2$), 2.80 (t, 2H, $-CH_2$), 3.65 (t, 4H, 2 x $-CH_2$), 4.15 (t, 2H, $-CH_2$), 6.82-6.85 (m, 1H, Ar-H), 7.13-7.70 (m, 13H, Ar-H), 12.22 (brs, 1H, -NH). ESI-MS : *m/z* = 426 $[M+H]^+$.

4-(2-Bromoethoxy)benzaldehyde (9a):
Prepared following the procedure described for **3** using 4-hydroxybenzaldehyde (3.10 g, 25.4 mmol), 1,2-dibromoethane (19.07 g, 101.5 mmol) and methanol (60 mL) to obtain the titled compound **9a** (3.15 g, 52%) as white solid. Mp: 54-56 ^{0}C. IR (KBr): υ3346, 2925, 1600 cm^{-1}. ^1H NMR ($CDCl_3$):δ 3.62 (t, 2H, $-CH_2$), 4.34 (t, 2H, -

CH_2), 7.02 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.81 (d, *J* = 8.25 Hz, 2H, Ar-H), 9.80 (s, 1H, -CHO). EI-MS : m/z 229 $[M]^+$.

4-(2-Bromoethoxy)-3-methoxybenzaldehyde (9b):
Prepared following the procedure described for **3** using 4-(3-methoxy) hydroxybenzaldehyde (4.0 g, 26.1 mmol), 1,2-dibromoethane (19.59 g, 104.3 mmol) and methanol (60 mL) to obtain the titled compound **9b** (3.78 g, 56%) as white crystalline solid. Mp: 66-67 ^{0}C. IR (KBr): υ3345, 1680, 1270 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ 3.64 (t, 2H, -CH_2), 3.90 (s, 3H, -OCH_3), 4.34 (t, 2H, -CH_2), 6.94 (d, *J* = 8.25 Hz, 2H, Ar-H), 7.34-7.40 (m, 2H, Ar-H), 9.80 (s, 1H, -CHO). ESI-MS : m/z 261 $[M + H]^+$.

4-(2-Dimethylaminoethoxy)benzaldehyde (10a):
Prepared following the procedure described for **5a** using 4-(2-bromoethoxy)-benzaldehyde (1.00 g, 4.36 mmol), 40% dimethylamine solution (10 mL, 81.6 mmol) and methanol (25 mL) to obtain the title compound **10a** (0.75 g, 89%) as brown liquid. IR (Neat): υ3435, 1690, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ 2.30 (s, 6H, 2 × CH_3), 2.76 (t, 2H, -CH_2), 4.15 (t, 2H, -CH_2), 7.00-7.05 (m, 2H, Ar-H), 7.35-7.36 (m, 2H, Ar-H), 9.80 (s, 1H, -CHO). EI-MS : m/z 193 $[M]^+$.

4-(2-Dimethylaminoethoxy)-3-methoxybenzaldehyde (10b):
Prepared following the procedure described for **5a** using 4-(2-bromoethoxy)-3-methoxybenzaldehyde (2.0 g, 7.68 mmol), 40% dimethylamine solution (20 mL, 163.2 mmol) and methanol (60 mL) to obtain the title compound **10b** (1.28 g, 74%) as pale yellow syrup. IR (Neat): υ2940,1685, 1270 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ 2.30 (s, 6H, 2 × CH_3), 2.75 (t, 2H, -CH_2), 3.89 (s, 3H, -OCH_3), 4.13 (t, 2H, -CH_2), 6.95 (d, 1H, Ar-H), 7.35 (d, 2H, Ar-H), 9.80 (s, 1H, -CHO).EI-MS : m/z 224 $[M]^+$.

Preparation of 4-(2-piperidinoethoxy)benzaldehyde (10c):
Prepared following the procedure described for **(5b)** using 4-(2-bromoethoxy)-benzaldehyde (0.85 g, 3.71 mmol), piperidine (40 mg, 4.70 mmol) and methanol (10 mL) to obtain the titled compound **10c** (41 mg, 95%) as brown syrup. IR (Neat): υ 2930, 1690, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6):δ 1.42-1.62 (m, 6H, 3 × CH_2), 2.45 (t, 4H, 2 x -CH_2), 2.76 (t, 2H, -CH_2), 4.10 (t, 2H, -CH_2), 7.16 (m, 2H, Ar-H), 7.35-7.42 (m, 2H, Ar-H), 9.90 (s, 1H, -CHO). ESI-MS : m/z 234 $[M + H]^+$.

Preparation of 4-(2-piperidinoethoxy)-3-methoxybenzaldehyde (10d):
Prepared following the procedure described for **(5b)** using 4-(2-bromoethoxy)-3-methoxybenzaldehyde (100 mg, 3.84 mmol), piperidine (81 mg, 9.41 mmol) and methanol (10 mL) to obtain the titled compound **10d** (80 g, 79%) as brown syrup. IR (Neat): υ2934, 1683, 1269 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ 1.42-1.48 (m, 2H, -CH_2), 1.63 (m, 4H, 2 x -CH_2), 2.52 (t, 4H, 2 x -CH_2), 2.82 (t, 2H, -CH_2), 3.90 (s, 3H, -OCH_3), 4.16 (t, 2H, -CH_2), 6.92 (d, *J* = 7.52 Hz, 1H, Ar-H), 7.38 (m, 2H, Ar-H), 9.82 (s, 1H, -CHO). ESI-MS : m/z 264 $[M+H]^+$.

Preparation of 4-(2-morpholinoethoxy)benzaldehyde (10e):
Prepared following the procedure described for **(5b)** using 4-(2-bromoethoxy)-benzaldehyde (50 mg, 2.15 mmol), morpholine (53 mg, 6.9 mmol) and methanol (15 mL) to obtain the titled compound **10e** (45 mg, 90%) as brown syrup. IR (Neat):υ 2950, 1685, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ2.53 (t, 4H, 2 x -CH_2), 2.82 (t, 2H, -CH_2), 3.66 (t, 4H, 2 x -CH_2), 4.16 (t, 2H, -CH_2), 6.93-7.00 (d, *J* = 9.00 Hz, 2H, Ar-H), 7.82 (d, *J* = 8.35 Hz, 2H, Ar-H), 9.80 (s, 1H, -CHO). ESI-MS : m/z 236 $[M+H]^+$.

Preparation of 4-(2-morpholinoethoxy)-3-methoxybenzaldehyde (10f):
Prepared following the procedure described for **(5b)** using, 4-(2-bromoethoxy)-3-methoxybenzaldehyde (50 mg, 1.92 mmol), morpholine (46 mg, 5.35 mmol) and methanol (15 mL) to obtain the titled compound **10f** (45 mg, 88%) as brown syrup. IR (Neat): υ2925, 1680,1269 cm^{-1}. ^{1}H NMR ($CDCl_3$):δ2.55 (t, 4H, 2 x -CH_2), 2.85 (t, 2H, -CH_2), 3.64 (t, 4H, 2 x -CH_2), 3.90 (s, 3H, -OCH_3), 4.16 (t, 2H, -CH_2), 6.90 (d, *J* = 9.00 Hz, 1H, Ar-H), 7.35 (d, *J* = 8.35 Hz, 2H, Ar-H), 9.82 (s, 1H, -CHO). ESI-MS : m/z 266 $[M+H]^+$.

Preparation of 2-(4-[2-dimethylaminoethoxy)phenyl]-4,5-diphenylimidazole (11a):
Prepared following the procedure described for **(7a)** using benzil (20 mg, 0.95 mmol), 4-(2-dimethylaminoethoxy) benzaldehyde (20 mg, 10.26 mmol), ammoniumacetate (20 mg, 2.57 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound **11a** (32 mg, 76.97%) as pale brown solid. Mp: 118-121 ^{0}C. IR (Neat): υ3055, 2925, 1490 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6):δ 2.30 (s, 6H, 2 × CH_3), 2.70 (t, 2H, -CH_2), 4.00 (t, 2H, -CH_2), 6.88 (d, *J* = 6.80Hz, 3H, Ar-H), 7.20-7.25 (m, 5H, Ar-H), 7.50 (d, *J* = 7.50Hz, 4H, Ar-H), 7.94 (d, *J* = 10.94Hz, 2H, Ar-H). ESI-MS : m/z 384 $[M+H]^+$. Anal.cacld.for: $C_{25}H_{25}N_30$: C, 78.30; H, 6.57. Found: C, 78.34; H, 6.60.

Preparation of 2-(4-[2-dimethylaminoethoxy)-3-methoxyphenyl]-4,5-diphenylimidazole
benzil (45 mg, 2.14 mmol), 4-(2-dimethylaminoethoxy)-3-methoxybenzaldehyde (50 mg, 2.27 mmol), ammonium acetate (55 mg, 7.12 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound **11b** (60 mg, 66%) as white solid. Mp: 186-188 ^{0}C. IR (KBr): υ3383, 1500, 1265 cm^{-1}. ^{1}H NMR (DMSO-d_6):δ 2.32 (s, 6H, 2 × CH_3), 2.70 (t, 2H, -CH_2), 3.90 (s, 3H, -OCH_3), 4.00 (t, 2H, -CH_2), 6.95 (d, J = 6.80 Hz, 1H, Ar-H), 7.20-7.42 (m, 5H, Ar-H), 7.50-7.70 (m, 7H, Ar-H). ESI-MS : m/z 414 [M+H]$^+$. Anal.cacld.for: $C_{26}H_{27}N_30_2$: C, 75.48; H, 6.51. Found: C, 75.46; H, 6.62.

Preparation of 2-(4-[2-(piperidino)ethoxy)phenyl]-4,5-diphenylimidazole (11c):
Prepared following the procedure described for **(7a)** using benzil (45 mg, 2.14 mmol), 4-(2-piperidinoethoxy)-benzaldehyde (55 mg, 2.27 mmol), ammoniumacetate (55 mg, 7.12 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound **11c** (55 mg, 60.39%) as brown solid. Mp: 189-192 ^{0}C. IR (Neat): υ3418, 1650, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6):δ 1.36 (m, 6H, 3 × CH_2), 2.51 (t, 4H, 2 x -CH_2), 2.75 (t, 2H, -CH_2), 4.10 (t, 2H, -CH_2), 6.88-6.92 (d, J = 8.80 Hz, 2H, Ar-H), 7.20-7.30 (m, 6H, Ar-H), 7.50-7.54 (d, J = 7.45 Hz, 4H, Ar-H), 7.96-8.00 (m, 2H, Ar-H). ESI-MS : m/z 424 [M + H]$^+$. Anal.cacld.for: $C_{28}H_{29}N_30$: C, 79.40; H, 6.89. Found: C, 79.44; H, 6.96.

Preparation of 2-(4-[2-(piperidino)ethoxy)-3-methoxyphenyl]-4,5-diphenylimidazole (11d):
Prepared following the procedure described for **(7a)** using benzil (45 mg, 2.14 mmol), 4-(2-piperidinoethoxy)-3-methoxybenzaldehyde (60 mg, 2.27 mmol), ammonium acetate (55 mg, 7.12 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound **11d** (56 mg, 56%) as yellow solid. Mp: 102-103 ^{0}C. IR (Neat): υ3420, 1645, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6):δ 1.42-1.60 (m, 6H, 3 × CH_2), 2.50 (t, 4H, 2 x -CH_2), 2.80 (t, 2H, -CH_2), 3.86 (s, 3H, -OCH_3), 4.12 (t, 2H, -CH_2), 5.00 (brs, 1H,-NH), 6.86 (d, J = 8.80 Hz, 1H, Ar-H), 7.20-7.32 (m, 6H, Ar-H), 7.50-7.65 (m, 6H, Ar-H). ESI-MS : m/z 454 [M + H]$^+$. Anal.cacld.for: $C_{29}H_{31}N_30_2$: C, 76.79; H, 6.88. Found: C, 76.85; H, 6.86.

Preparation of 2-(4-[2-(morpholino)ethoxy)phenyl]-4,5-diphenylimidazole (11e):
Prepared following the procedure described for **(7a)** using benzil (45 mg, 2.14 mmol), 4-(2-morpholinoethoxy) benzaldehyde (55 mg, 2.27 mmol), ammoniumacetate (55 mg, 7.12 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound (58 mg, 62.46%) **(11e)** as brown semisolid. IR (Neat):υ 3060, 1603, 1246 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6):δ 2.55 (t, 4H, 2 x -CH_2), 2.77 (t, 2H, -CH_2), 3.68 (t, 4H, 2 x -CH_2), 4.14 (t, 2H, -CH_2), 6.90 (d, J = 8.86 Hz, 2H, Ar-H), 7.20-7.57 (m, 10H, Ar-H), 8.00 (m, 2H, Ar-H). ESI-MS : m/z 426 [M +H]$^+$. Anal.cacld.for : $C_{27}H_{27}N_30_2$: C, 76.28; H, 6.31. Found: C, 76.30; H, 6.36.

Preparation of 2-(4-[2-(morpholino)ethoxy)-3-methoxyphenyl]-4,5-diphenyimidazole (11f):
Prepared following the procedure described for **(7a)** using, benzil (45 mg, 2.14 mmol), 4-(2-morpholinoethoxy)-3-methoxybenzaldehyde (55 mg, 2.27 mmol), ammonium acetate (55 mg, 7.12 mmol), catalyst TBAHS (30 mol%) to obtain the titled compound **11f** (45 mg, 54.75%) as brown solid. Mp: 196-199 ^{0}C. IR (Neat): υ3060, 2936, 1500 cm^{-1}. ^{1}H NMR (DMSO-d_6):δ 2.50-2.55 (m, 4H, 2 x -CH_2), 2.70 (t, 2H, -CH_2), 3.58 (t, 4H, 2 x -CH_2), 3.90 (s, 3H, -OCH_3), 4.10 (t, 2H, -CH_2), 6.90-7.63 (m, 13H, Ar-H), 12.35 (brs, 1H, -NH).ESI-MS : m/z 456 [M+H]$^+$. Anal.cacld.for: $C_{28}H_{29}N_30_3$: C, 73.82; H, 6.41. Found: C, 73.77; H, 6.58.

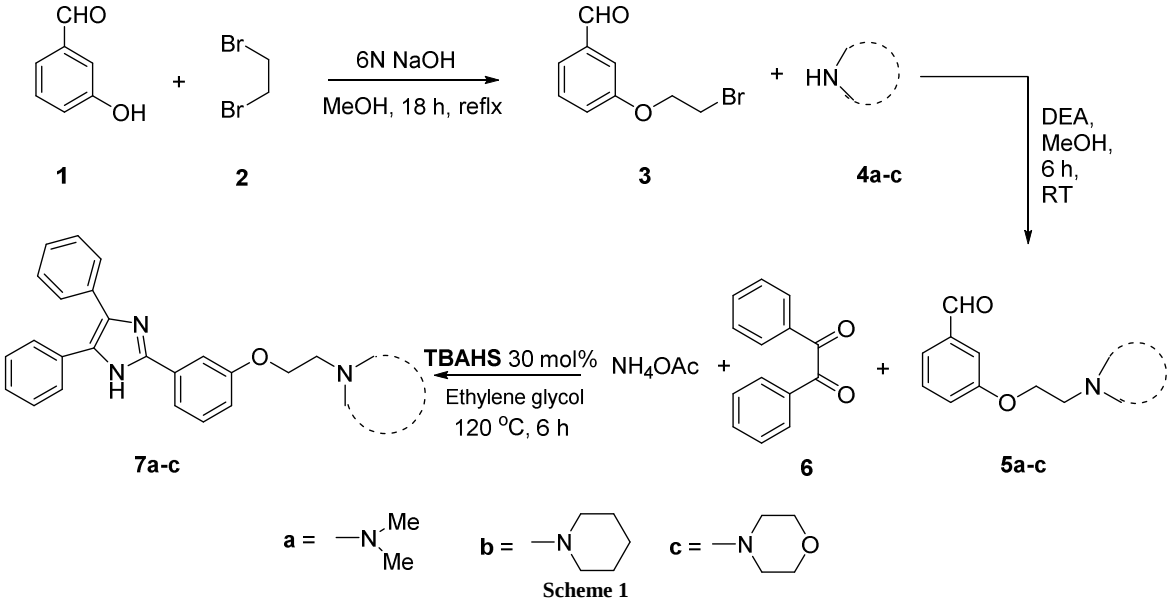
RESULTS AND DISCUSSION

Synthesizing analogues of biologically active molecules is an enhancement for the drug discovery and a basic requirement in synthetic organic chemistry. One such pharmacologically potent 2,4,5-triarylimidazole is trifenagrel that inhibits both arachidonate and collagen induced aggregation of platelets. In the present work, we have undertaken the synthesis of analogues of trifenagrel.

In the course of the studies directed towards the synthesis of analogues of trifenagrel we had selected three substituted benzaldehydes namely 3-hydroxy benzaldehyde, 4-hydroxybenzaldehyde and vanillin. These benzaldehydes were first treated with dibromoethane to afford corresponding bromoethoxybenzaldehydes which on subsequent reaction with different amines (dimethylamine, piperidine, morpholine) furnished corresponding aminoethoxybenzaldehydes. Condensation of aminoethoxy benzaldehydes with benzil and ammonium acetate using catalytic amount of *tetrabutylammonium hydrogen sulphate (TBAHS)* resulted in the desirable analogues of trifenagrel. Nine analogues were synthesized and characterized by their IR, ^{1}H NMR, Mass spectrums.

We used TBAHS as the phase transfer catalyst, being acidic in nature and it performs many organic transformations under mild conditions. It has been used for dehydration and cyclization step in Hantzsh dihydropyridine synthesis and it is easy to handle, inexpensive, water soluble and thermally stable. [7-8]

Following our plan of sketch for the synthesis of analogues of trifenagrel we initially prepared 3-aminoethoxy phenyl substituted trisubstituted imidazole derivatives **(7a-c)**. Accordingly reaction of 3-hydroxybenzaldehyde **(1)** with dibromoethane **(2)** in the presence of 6N NaOH gave 3-(2-bromoethoxy) benzaldehyde **(3)** in 50% yield as brown liquid. The formation of the compound was evident from mass spectrum (EI) by the appearance of molecular ion peak at *m/z* 228, IR by the appearance of C-H stretching of CHO at 1695 cm^{-1} , ^1H NMR by the appearance of methylene protons at δ 3.58 and δ 4.24 as triplets. The compound **(3)** was then treated with dimethylamine in the presence of methanol to afford compound **(5a)** in 90% yield as yellow solid. In the mass spectrum (EI) the appearance of molecular ion peak at *m/z* 193, in IR the appearance of C-H stretching of CHO at 1679 cm^{-1} and appearance of a singlet at δ 2.90 corresponding to methyl protons of amine in ^1H NMR confirmed the compound **(5a).**



Scheme 1

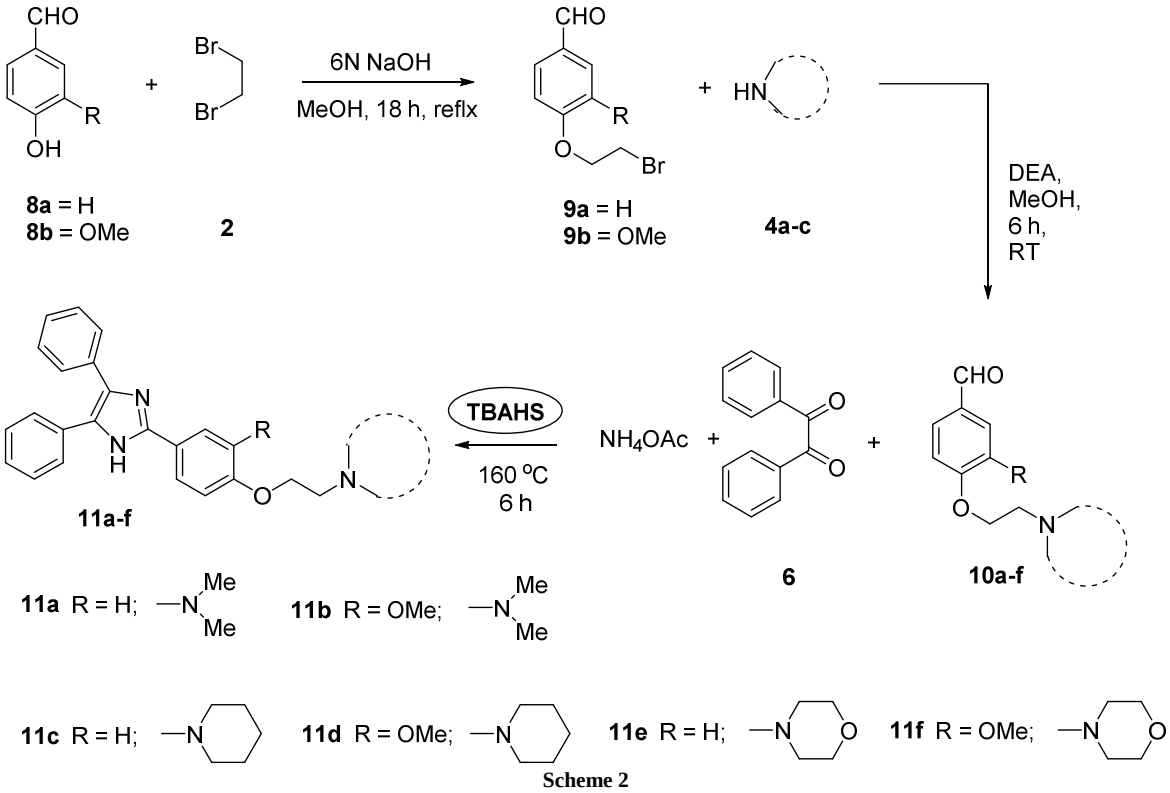
Similarly two more derivatives **(5b, 5c)** were prepared from compound **(3).** 3-(2-piperidinoethoxy) benzaldehyde was obtained in 68% yield as brown liquid by the reaction of piperidine with compound **(3).** The compound **(5b)** was structurally confirmed by the appearance of $[M+H]^+$ peak at *m/z* 234 in mass spectrum (ESI), C-H stretching of CHO at 1697 cm^{-1} in IR and the appearance of aliphatic protons of piperidine at δ 1.46 and δ 3.46 as multiplet and triplet respectively in ^1H NMR. In an identical manner compound **(5c)** was prepared with 70% yield as brown liquid and the spectroscopic features fully supported its assigned structure.

The three-component condensation of benzil **(6),** aldehydes **(5a-c)** and ammonium acetate in the presence of 30 mol% of TBAHS gave trisubstituted imidazoles **(7a-c)(Scheme-1).** The compound **(7a)** was characterized from mass spectrum (ESI) by appearance of $[M+H]^+$ peak at *m/z* = 384, IR by the appearance of N-H band at 3423 cm^{-1} and from ^1H NMR by the appearance of increased aromatic protons at δ 7.20-7.60 and the absence of CHO proton at δ 10.00. Similarly the compounds **(7b, 7c)** were synthesized and their spectroscopic features fully supported the assigned structures.

The scope of the reaction was further extended for the preparation of 4-hydroxybenzaldehyde and vanillin derived analogues of trifenagrel using compounds **(8a, 8b).** The compounds **(8a, 8b)** on reaction with 1,2-dibromoethane in the presence of 6N NaOH provided the compound **(9a, 9b)** respectively. The formation of compounds **(9a, 9b)** was evident from the appearance of $[M+H]^+$ peak at *m/z* = 230 and 250 in mass spectrum (ESI) respectively, C-H stretching of CHO at 1685 and 1680 cm^{-1} in IR respectively and the appearance of methylene protons as triplet at δ 3.65 and δ 4.35 respectively in ^1H NMR of both the compounds **(9a, 9b)**.

The compounds **(9a, 9b)** were then treated with dimethylamine in the presence of methanol to afford compound **(10a, 10b)** as brown liquid in 85% yield **(Scheme-2).** The formation of the compound **(10a, 10b)** was evident from the appearance of $[M+H]^+$ peak at *m/z* = 193 and 224 in mass spectrum (ESI) respectively, C-H stretching of CHO at 1692 and 1680 cm^{-1} in IR respectively and the appearance of a singlet at δ 2.32 and δ 2.30 respectively in ^1H NMR spectra corresponding to methyl protons of amine**.** In a similar way two more derivatives for each **(10c, 10d, 10e, 10f)** were synthesized and their spectroscopic features fully supported its assigned structure.

The three-component condensation of benzil **(6),** aldehydes **(10a-f)** and ammonium acetate in the presence of 30 mol% of TBAHS gave trisubstituted imidazoles **(11a-f) (Scheme-2).** The compound **(11a)** was characterized from mass spectrum (ESI) by appearance of $[M+H]^+$ peak at *m/z* = 384, IR by the appearance of N-H band at 3055 cm^{-1} and from ^1H NMR by the appearance of increased aromatic protons at δ 7.30-7.90 and the absence of CHO proton at δ 9.90. Similarly the compounds **(11b-f)** were synthesized and their spectroscopic features fully supported its assigned structure.



Scheme 2

CONCLUSION

We successfully synthesized analogues of trifenagrel and selected three substituted benzaldehydes. Condensation of aminoethoxy benzaldehydes with benzil and ammonium acetate using catalytic amount of tetrabutylammonium hydrogen sulphate (TBAHS) resulted in the desirable analogues of trifenagrel. Nine analogues were synthesized and characterized by their IR, ^1H NMR, Mass spectrums

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