Synthesis and characterization of novel iminobenzoates with terminal pyrazine moieties

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Abstract
Apart from its numerous biological activities like antidiabetic, anti-inflammatory, antimicrobial, pyrazine moiety plays an important role in luminescent materials. Its role in luminescent materials is due to its highly electron deficient nature specially when it is in the centre along the mainstay of extended π-conjugated systems. Similarly, new liquid crystalline compounds are being made constantly where the central benzoaromatic moiety is being replaced with the heterocycles including pyrazine due to their more variable nature. Pyrazine derivatives can also be used in supramolecular assemblies due to their efficient hydrogen bonding, protonation and complexation properties. Keeping in view the enormous applications of pyrazine derivatives we planned to synthesize new extended iminobenzoates with pyrazine moieties at the terminal positions. The planned iminobenzoates with terminal pyrazine moieties were prepared following standard procedures. The pyrazine-2-carbohydrazide (1) and 5-methylpyrazine-2-carbohydrazide (2) were prepared by refluxing their methyl esters with hydrazine hydrate in methanol. The esters (3a–3f) were synthesized by reacting 4-hydroxybenzaldehyde with differently substituted acid halides in tetrahydrofuran in the presence of triethyl amine. The target compounds that is, iminobenzoates with the pyrazine moieties at terminal positions (4a–4l), were obtained in good to excellent yields by the reaction of the hydrazides with the esters at reflux. The synthesized compounds were fully characterized using different spectroanalytical techniques including FT-IR, NMR, Mass, elemental analysis and single crystal X-ray diffraction analysis. The paper describes the synthesis of novel iminobenzoates following easy methods while utilizing commercially available starting materials. The synthesized iminobenzoates may possibly be converted to compounds with luminescent and liquid crystalline properties after making suitable changes to the pyrazine moieties. Properly substituted pyrazines on both sides, capable of further suitable extensions, may result in compounds with such properties.

Keywords: Pyrazine, Pyrazine-2-carbohydrazide, 5-Methylpyrazine-2-carbohydrazide, Triethyl amine, Iminobenzoates, X-ray crystallography

Introduction
Pyrazine belongs to the six members heterocyclic diazines with two nitrogen in the same ring at 1, 4 positions, the other members being the pyridazine and pyrimidine with the two nitrogens at 1, 2 and 1, 3 positions respectively [1–4]. Another pyrazine containing heterocycle is the quinoxaline or benzopyrazine. Both pyrazine and quinoxaline derivatives are quite important due to their crucial roles in natural and synthetic compounds [5–10].

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Melting points were determined via Bock-monoscop-M. Reagents and solvents used were of analytical grade.

Materials and methods

General

Reagents and solvents used were of analytical grade. Melting points were determined via Bock-monoscop-M.

Synthesis of pyrazine-2-carbohydrazides (1 and 2)

Pyrazine-2-carbohydrazide (1) and 5-methylpyrazine-2-carbohydrazide (2) were prepared following the literature known procedure [24].

General procedure for the synthesis of esters (3a–3f)

Aldehyde (8.0 mmol) was dissolved in tetrahydrofuran (40 mL) and triethyl amine (24.0 mmol) was added to it. The mixture was stirred for 15 min and then kept in an...
ice bath. Acid halide (8.0 mmol) dissolved in tetrahydrofuran (40 mL) was added dropwise to the reaction mixture. Reaction was stirred for 2 h and then filtered. The filtrate was concentrated and the residue was recrystallized from chloroform in petroleum ether.

4-Formylphenyl 2-fluorobenzoate (3b)

Colour: off-white solid; yield: 1.67 g, 6.4 mmol, 80%; Rf: 0.45 (40% acetone in n-hexane); mp 92–93 °C; IR (υ, cm⁻¹): 1728, 1699, 1253, 732; ¹H NMR (300 MHz, CDCl₃): δ 7.41–7.49 (3H, m, H-3,4,5), 7.55–7.57 (2H, m, H-2,2'), 7.98–8.03 (2H, m, H-1,1'), 8.07–8.10 (1H, m, H-6), 10.05 (1H, s, CHO).

4-Formylphenyl 3-chlorobenzoate (3c)

Colour: off-white solid; yield: 1.0 g, 3.8 mmol, 48%; Rf: 0.45 (40% acetone in n-hexane); mp 97–99 °C; IR (υ, cm⁻¹): 1728, 1699, 1253, 732; ¹H NMR (300 MHz, CDCl₃): δ 7.40 (2H, d, J = 8.4 Hz, H-2,2'), 7.47–7.49 (1H, m, H-5), 7.61–7.64 (1H, m, H-4), 7.97 (2H, d, J = 8.4 Hz, H-1,1'), 8.06–8.09 (1H, m, H-6), 8.17 (1H, s, H-3), 10.02 (1H, s, CHO).

4-Formylphenyl 4-chlorobenzoate (3d)

Colour: white crystals; yield: 1.57 g, 6.0 mmol, 75%; Rf: 0.45 (40% acetone in n-hexane); mp 116–118 °C; IR (υ, cm⁻¹): 1728, 1683, 1261, 746; ¹H NMR (300 MHz, CDCl₃): δ 7.43 (2H, d, J = 8.7 Hz, H-4,5), 7.53 (2H, d, J = 8.7 Hz, H-3,6), 8.00 (2H, d, J = 8.4 Hz, H-2,2'), 8.16 (2H, d, J = 8.4 Hz, H-1,1'), 10.05 (1H, s, CHO).

4-Formylphenyl 3-bromobenzoate (3e)

Colour: off-white solid; yield: 1.15 g, 3.8 mmol, 47%; Rf: 0.45 (40% acetone in n-hexane); mp 98–100 °C; IR (υ, cm⁻¹): 1728, 1697, 1253, 513; ¹H NMR (400 MHz, CDCl₃): δ 7.40 (2H, d, J = 8.4 Hz, H-2,2'), 7.41–7.42 (1H, m, H-5), 7.77–7.79 (1H, m, H-4), 7.97 (2H, d, J = 8.4 Hz, H-1,1'), 8.11–8.13 (1H, m, H-6), 8.33 (1H, s, H-3), 10.02 (1H, s, CHO).

4-Formylphenyl 4-bromobenzoate (3f)

Colour: off-white solid; yield: 1.76 g, 5.8 mmol, 72%; Rf: 0.45 (40% acetone in n-hexane); mp 172–174 °C; IR (υ, cm⁻¹): 1741, 1699, 1265, 520; ¹H NMR (400 MHz, CDCl₃): δ 7.39 (2H, d, J = 8.4 Hz, H-2,2'), 7.66 (2H, d, J = 8.4 Hz, H-4,5), 7.96 (2H, d, J = 8.4 Hz, H-3,6), 8.05 (2H, d, J = 8.4 Hz, H-1,1'), 10.01 (1H, s, CHO).

General procedure for the synthesis of iminobenzoates (4a–4l)

The hydrazide (3.00 mmol) was dissolved in methanol (50 mL) and added dropwise to a methanolic (50 mL) solution of the ester (3.00 mmol). Reaction mixture was refluxed for 5 h. The solid formed was filtered, washed with cold methanol, dried over anhydrous CaCl₂ under vacuum and recrystallized from chloroform in n-hexane.

4-[(E)-(Pyrazine-2-carboxylimino)methyl]phenyl 2-fluorobenzoate (4a)

Colour: white shiny crystals; yield: 0.6 g, 1.6 mmol, 56%; Rf: 0.3 (40% acetone in n-hexane); mp 281–290 °C; IR (υ, cm⁻¹): 3300, 1728, 1674, 1600, 1290, 1018; ¹H NMR (300 MHz, DMSO): δ 7.41–7.48 (4H, m, H-1,1',2,2'), 7.76–7.87 (3H, m, H-3,4,5), 8.09–8.15 (1H, m, H-6), 8.68 (1H, s, H=CN=N), 8.80 (1H, d, J = 2.4 Hz, H-5 pyrazine), 8.93 (1H, d, J = 2.4 Hz, H-6 pyrazine), 9.28 (1H, s, H-3 pyrazine), 12.36 (1H, s, CONH); MS (EI, m/z): 364 [M⁺], 243, 123, 109, 81, 61.

4-[(E)-(Pyrazine-2-carboxylimino)methyl]phenyl 2-chlorobenzoate (4b)

Colour: white shiny flakes; yield: 0.9 g, 2.4 mmol, 80%; Rf: 0.82 (50% acetone in n-hexane); mp 262–265 °C; IR (υ, cm⁻¹): 3288, 1743, 1674, 1560, 1244, 1199, 1020, 750; ¹H NMR (400 MHz, DMSO): δ 7.44 (2H, d, J = 8.4 Hz, H-2,2'), 7.54–7.58 (1H, m, H-3), 7.84–7.86 (2H, m, H-4,5), 7.85 (2H, d, J = 8.4 Hz, H-1,1'), 8.10–8.12 (1H, m, H-6), 8.69 (1H, s, H=CN=N), 8.80 (1H, d, J = 2.4 Hz, H-5 pyrazine), 8.93 (1H, d, J = 2.4 Hz, H-6 pyrazine), 9.27 (1H, s, H-3 pyrazine), 12.33 (1H, s, CONH); MS (EI, m/z): 380 [M⁺], 139, 123, 111, 75, 52.

4-[(E)-(Pyrazine-2-carboxylimino)methyl]phenyl 3-chlorobenzoate (4c)

Colour: Lemon green powder; yield: 1.0 g, 2.6 mmol, 89%; Rf: 0.41 (40% acetone in n-hexane); mp 265–272 °C; IR (υ, cm⁻¹): 3302, 1728, 1678, 1610, 1261, 1020, 736; ¹H NMR (400 MHz, DMSO): δ 7.44 (2H, d, J = 8.4 Hz, H-2,2'), 7.64–7.68 (1H, m, H-3), 7.83–7.85 (3H, m, H-4,5,6), 8.10 (2H, d, J = 8.4 Hz, H-1,1'), 8.69 (1H, s, H=CN=N), 8.80 (1H, d, J = 2.4 Hz, H-5 pyrazine), 8.93 (1H, d, J = 2.4 Hz, H-6 pyrazine), 9.27 (1H, s, H-3 pyrazine), 12.32 (1H, s, CONH); MS (EI, m/z): 380 [M⁺], 139, 123, 111, 80, 52.
4-(E)-(Pyrazine-2-carboxylimino)methyl[phenyl]

3-bromobenzoate (4e)

Colour: white crystals; yield: 0.55 g, 1.3 mmol, 44%; Rf: 0.5 (40% acetone in n-hexane); mp 252–260 °C; IR (v, cm⁻¹): 3292, 1732, 1674, 1591, 1253, 1197, 1012, 738; ¹H NMR (400 MHz, DMSO): δ 7.42 (2H, d, J = 8.4 Hz, H-2,2'), 7.70 (2H, d, J = 8.4 Hz, H-1,1'), 7.84 (2H, d, J = 8.4 Hz, H-4,5'), 8.15 (2H, d, J = 8.4 Hz, H-3,6'); 8.68 (1H, s, HNC=N), 8.80 (1H, d, J = 2.4 Hz, H-5 pyrazine), 8.93 (1H, d, J = 2.4 Hz, H-6 pyrazine), 9.27 (1H, s, H-3 pyrazine), 12.32 (1H, s, CONH); MS (El, m/z): 380 [M⁺], 139, 123, 111, 80, 44.

4-(E)-(Pyrazine-2-carboxylimino)methyl[phenyl]

4-bromobenzoate (4f)

Colour: white shiny crystals; yield: 0.92 g, 2.3 mmol, 77%; Rf: 0.41 (40% acetone in n-hexane); mp 253–260 °C; IR (v, cm⁻¹): 3302, 1728, 1678, 1602, 1257, 1199, 1020, 721; ¹H NMR (400 MHz, DMSO): δ 7.43 (2H, d, J = 8.4 Hz, H-2,2'), 7.64–7.68 (1H, m, H-3), 7.82–7.85 (3H, m, H-4,5,6), 8.10 (2H, d, J = 8.4 Hz, H-1,1'), 8.68 (2H, s, HNC=N, H-6 pyrazine), 9.13 (1H, s, H-3 pyrazine), 12.25 (1H, s, CONH); MS (El, m/z): 394 [M⁺], 139, 121, 111, 94, 75.

4-(E)-(5-Methylpyrazine-2-carboxylimino)methyl[phenyl]

3-chlorobenzoate (4i)

Colour: Lemon green powder; yield: 0.92 g, 2.3 mmol, 77%; Rf: 0.42 (40% acetone in n-hexane); mp 250–257 °C; IR (v, cm⁻¹): 3302, 1728, 1678, 1560, 1261, 1012, 752; ¹H NMR (400 MHz, DMSO): δ 7.43 (2H, d, J = 8.4 Hz, H-2,2'), 7.64–7.68 (1H, m, H-3), 7.82–7.85 (3H, m, H-4,5,6), 8.10 (2H, d, J = 8.4 Hz, H-1,1'), 8.68 (2H, s, HNC=N, H-6 pyrazine), 9.13 (1H, s, H-3 pyrazine), 12.25 (1H, s, CONH); MS (El, m/z): 394 [M⁺], 139, 121, 111, 94, 75.
Results and discussion

The target compounds (4a–4l) were successfully synthesized by reacting hydrazides (1 and 2) with the esters (3a–3f) formed themselves by the reaction of 4-hydroxybenzaldehyde with differently substituted benzoyl chlorides (Scheme 1).

Synthesis of the target compounds was carried out according to scheme 1. Hydrazides 1 and 2 were synthesized following the literature known method [24]. The esters (3a–3f) were synthesized by reacting 4-hydroxybenzaldehyde with different halogenated benzoyl chlorides in an equimolar ratio. Ranges for the C=O moiety of the ester linkage in the IR spectra of different esters were observed at 1728–1745 cm$^{-1}$ while for its C–O linkage the peaks were noticed at 1253–1265 cm$^{-1}$. Similarly, aldehydic C=O bond displayed the peaks in the range of 1683–1699 cm$^{-1}$ in different esters. C–X (X = halogens) bonds gave their peaks at 513–1207 cm$^{-1}$. Further confirmation to the successful synthesis of the esters was made with NMR studies and the data was consistent with the literature known data [33–35].

The synthesized esters were treated with the hydrazides 1 and 2 in an equimolar ratio resulting in the target iminobenzoates (4a–4l) in good to excellent yields. Their successful synthesis was confirmed using different spectroanalytical techniques. In the IR spectra, prominent peaks were observed for the NH group of amide linkages in the range of 3284–3304 cm$^{-1}$ while its carbonyl moiety (C=O) displayed peaks in the range of 1670–1683 cm$^{-1}$. The carbonyl group of the ester functionality in different iminobenzoates gave very strong peaks in the range of 1716–1743 cm$^{-1}$. The peaks for the aldehydic moiety were not observed in the final products after being converted to the imine (C=N) group which is also a strong proof for the successful synthesis of the target compounds. Peaks for the new imine functionality were observed in the range of 1560–1610 cm$^{-1}$ in different final products. NMR studies further confirmed the successful synthesis of our target compounds. The proton of the newly formed azomethine (HC=N) functionality resonated in the proton NMR spectra in the

![Scheme 1](image-url)

Scheme 1 Synthesis of extended iminobenzoates with terminal pyrazine moieties

$\text{CHO} + \text{COCl} \rightarrow \text{Et}_3\text{N} \rightarrow \text{THF} \rightarrow \text{OHC} + \text{O} \rightarrow \text{CH}_3\text{OH} \rightarrow \text{N} \rightarrow \text{N} \rightarrow \text{R}

3a: X = 2-F
3b: X = 2-Cl
3c: X = 3-Cl
3d: X = 4-Cl
3e: X = 3-Br
3f: X = 4-Br

4a: R = H; X = 2-F
4b: R = H; X = 2-Cl
4c: R = H; X = 3-Cl
4d: R = H; X = 4-Cl
4e: R = H; X = 3-Br
4f: R = H; X = 4-Br
4g: R = CH$_3$; X = 2-F
4h: R = CH$_3$; X = 2-Cl
4i: R = CH$_3$; X = 3-Cl
4j: R = CH$_3$; X = 4-Cl
4k: R = CH$_3$; X = 3-Br
4l: R = CH$_3$; X = 4-Br
range of 8.68–8.69 ppm. Similarly, the proton of the amide linkage gave prominent resonance in the range of 12.24–12.36 ppm.

Mass spectra (EIMS) displayed the exact molecular ion peaks for all the synthesized compounds while elemental analysis (Table 1) further aided in the confirmation of the successful synthesis of the target molecules.

X-ray diffraction analysis stamped well the successful synthesis of the final compounds. Figure 1 and Table 2 shows the XRD structures and main structural parameters of compounds 4d and 4j—a further proof to the successful synthesis of these compounds.

Both structures show similar spatial conformation, but with different structural behavior for each side of the central phenyl group (Fig. 1). The pyrazine ring and carbohydrazide system are almost coplanar, with calculated dihedral angles between mean planes of 9.63° and 9.35° for compounds 4d and 4j, respectively, and these groups are also coplanar with respect to central phenyl ring. On the other side of the molecule, the dihedral angles between mean planes of central phenyl ring and benzoate moiety is 48.23° for 4d of 56.25° for 4j. Packing of 4d is governed by weak hydrogen bond, which builds a one-dimensional polymeric structure parallel to [100] direction, and by π–π-stacking interactions between two units of neighboring pyrazine rings intercalated by one central phenyl ring, forming a layer parallel to crystallographic plane (Fig. 1). In the case of 4j, packing is

| Compound | Molecular formula | Molecular weight | Calculated (%) | Found (%) |
|----------|------------------|-----------------|---------------|----------|
|          |                  |                 | C  | H  | N  | C  | H  | N  |
| 4a       | C_{19}H_{13}FN_{4}O_{3} | 364.33 | 62.64 | 3.60 | 15.38 | 62.83 | 3.78 | 15.10 |
| 4b       | C_{19}H_{13}ClN_{4}O_{3} | 380.78 | 59.93 | 3.44 | 14.71 | 59.64 | 3.08 | 14.89 |
| 4c       | C_{19}H_{13}ClN_{4}O_{3} | 380.78 | 59.93 | 3.44 | 14.71 | 60.13 | 3.21 | 14.93 |
| 4d       | C_{19}H_{13}ClN_{4}O_{3} | 380.78 | 59.93 | 3.44 | 14.71 | 60.30 | 3.70 | 14.84 |
| 4e       | C_{19}H_{13}ClN_{4}O_{3} | 425.24 | 53.67 | 3.08 | 13.18 | 53.58 | 2.90 | 13.32 |
| 4f       | C_{19}H_{13}BrN_{4}O_{3} | 425.24 | 53.67 | 3.08 | 13.18 | 53.79 | 3.21 | 13.35 |
| 4g       | C_{20}H_{15}FN_{4}O_{3} | 378.36 | 63.49 | 4.00 | 14.81 | 63.67 | 4.19 | 14.69 |
| 4h       | C_{20}H_{15}ClN_{4}O_{3} | 394.81 | 60.84 | 3.83 | 14.19 | 60.68 | 3.59 | 14.40 |
| 4i       | C_{20}H_{15}ClN_{4}O_{3} | 394.81 | 60.84 | 3.83 | 14.19 | 60.72 | 3.97 | 14.51 |
| 4j       | C_{20}H_{15}ClN_{4}O_{3} | 394.81 | 60.84 | 3.83 | 14.19 | 61.13 | 4.09 | 14.01 |
| 4k       | C_{20}H_{15}BrN_{4}O_{3} | 439.26 | 54.69 | 3.44 | 12.75 | 54.38 | 3.35 | 12.98 |
| 4l       | C_{20}H_{15}BrN_{4}O_{3} | 439.26 | 54.69 | 3.44 | 12.75 | 54.82 | 3.71 | 12.53 |

**Fig. 1 X-ray diffraction structures of compounds 4d and 4j**
mainly governed π–π-stacking interactions, which were observed between neighboring pyrazine rings forming pairs of molecules related by center of symmetry (Fig. 2).

**Conclusion**

The novel iminobenzoates with terminal pyrazine moieties were successfully synthesized while using easily available starting materials. The synthesized compounds were characterized with the help of different spectroanalytical techniques (IR, MS, NMR CHNS, and XRD). The synthesis may provide a useful route to extended π-conjugated systems having central pyrazine moieties in their backbone. Intramolecular charge transfer (ICT) resulted due to the highly π-electron deficient nature of pyrazines would ultimately cause these compounds luminescent. These compounds may also display LC
properties if central pyrazines are properly substituted on both the sides.

Authors’ contributions
MA devised, supervised the whole work and wrote the manuscript. AJB run and interpreted the XRDs and contributed to manuscript writing. All the other authors ZP, SH, MRS, MT, GD, MS, MTJ, and MA contributed to one and/or other part of experimental and spectroscopic studies. All authors read and approved the final manuscript.

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