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Original article

Synthesis of biologically active *N*-methyl derivatives of amidines and cyclized five-membered products of amidines with oxalyl chloride

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Abstract

A series of substituted *N*-methylisonicotinamidine (**2a–f**), *N*-methylpyrazine-2-carboxamidine (**2g–i**) derivatives were synthesized by reaction of amidine derivatives (**1a–i**) with methyl iodide in presence of triethylamine. Five-membered condensed dihydroimidazolylbenzenesulfonamide derivatives (**3a–i**) were obtained by the reaction of amidine derivatives (**1a–i**) with acylating agent oxalyl chloride. All the compounds, i.e. **2a–i** and **3a–i** were purified by crystallization. Structures of all the synthesized compounds are supported by correct IR, ^{1}H NMR, mass spectral and analytical data. Anti-inflammatory activity evaluation was carried out using carrageenan-induced paw oedema assay and compounds **2e**, **3a** and **3d** exhibited good anti-inflammatory activity (44%, 31% and 37% activity at 50 mg/kg p.o., respectively). Analgesic activity evaluation was carried out using acetic acid writhing assay and compounds **2a** and **3f** gave 75% activity each at 100 mg/kg p.o.; on the other hand compounds **3a** and **3d** exhibited 60% analgesic activity each at 50 mg/kg p.o. Compounds **3a** and **3d** exhibited good anti-inflammatory and analgesic activities.

Keywords: Methyl iodide; Oxalyl chloride; Acylating agent; Anti-inflammatory; Analgesic

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications for the treatment of pain, management of oedema and tissue damage resulting from inflammatory joint disease (arthritis). The major limiting side effects of chronic use of NSAIDs are gastrointestinal (GI) symptoms and bleeding ulceration [1,2]. The identification of cyclooxygenase-2 (COX-2) and the subsequent introduction of the COX-2 selective inhibitor NSAID drugs were thought to be a major breakthrough, with the expectation of a significant reduction in GI side effects. It has now been proved that COX-2 inhibitors cause oedema, hypertension and congestive heart failure [3]. These observations raised a cautionary flag in this research. There is a demand for more efficacious and safer anti-inflammatory drugs with higher patient acceptability to completely abandon the use of steroidal and narcotic drugs. Derivatives comprising the sulfonamide functionalities act as anticancer agents [4], inhibitors of the serine protease human leukocyte elastase (HLE), proteinase 3 (PR 3) and cathepsin G (Cat G) [5]. Their use as anti-inflammatory analgesic agents [6], inhibitors of metallo-β-lactamases [7] is also reported in the literature. In continuation of our efforts in this direction to explore safer non-steroidal anti-inflammatory drugs [8–14] we have synthesized various compounds, i.e imidazoline diones [15–21], *N*-methylpicolinamidine and *N*-methylisonicotinamidine derivatives [22,23]. These were then screened for anti-inflamamtory and analgesic activities which we wish to report in this paper.

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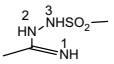
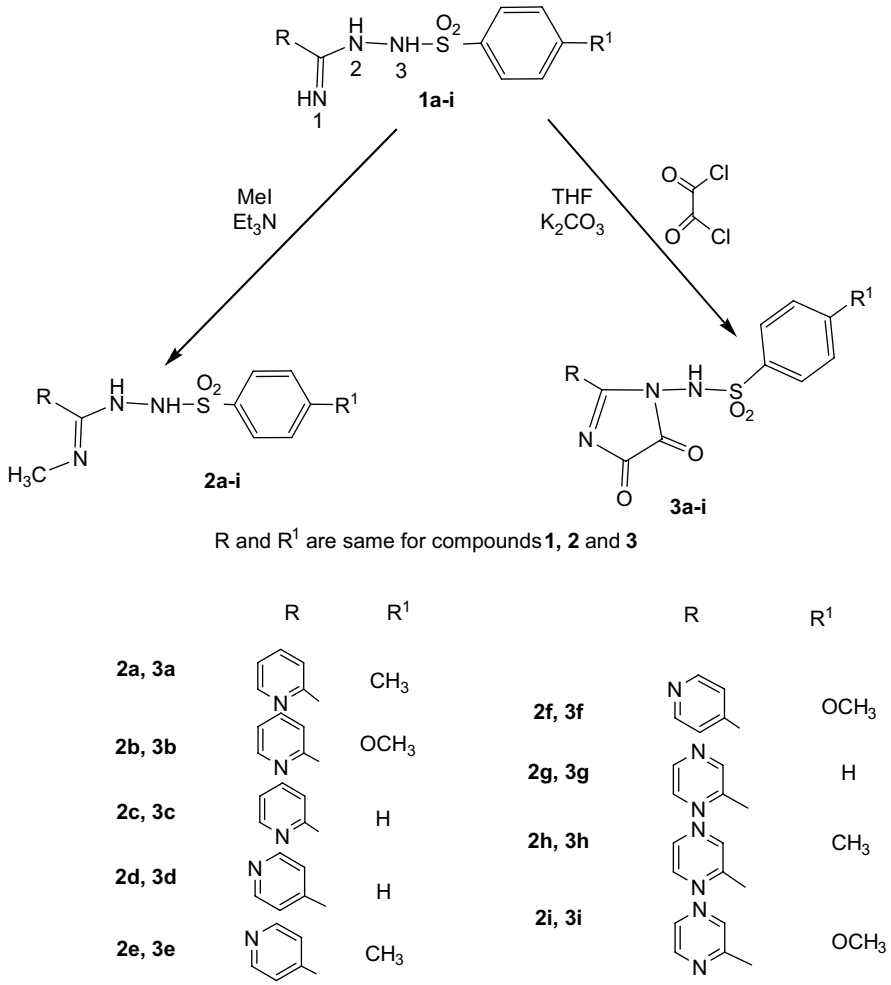
2. Results and discussion

2.1. Chemistry

Amidine derivatives **1a–i** (Scheme 1) were synthesized by following the reaction procedure reported earlier [24]. A look at amidine molecule **1** (Scheme 1) indicates that there are three nitrogens i.e. N1, N2 and N3 present in the molecule. Since $-SO_2-$ present in the molecule is electron withdrawing in nature, its electron withdrawing inductive effect (−I) will increase when we move from N1 → N2 → N3 thus nucleophilic character of these three nitrogens will be N1 > N2 > N3. Similar observation is also mentioned in literature [25,26]. From this observation it is expected that mono-alkylation will occur on N1 and if we have bifunctional acylating agent such as oxalyl chloride [15–17], attack will occur on N1 and N2, thus forming a five-membered ring structure. With these observations in mind we alkylated amidine derivatives with methyl iodide/Et_3N and acylated with oxalyl chloride, which is described here. ^{1}H NMR (500 MHz; DMSO-d_6) of **1a** shows a broad singlet at δ 6.47 accounting for two protons which are exchangeable with D_2O. Evidently these protons belong to N1 and N2 of  moiety of **1a**. Compound **1a** was treated with methyl iodide in the presence of triethylamine at room temperature for 2 h using methanol as a solvent of the reaction. After 2 h the solvent was removed under reduced pressure and the crude mass so obtained was taken in ethylacetate; this ethylacetate solution was washed with water. Organic layer so obtained was dried on sodium sulphate and solvent was removed under reduced pressure. The crude product so obtained was crystallized from methanol/ethylacetate to give pure product **2a** (Scheme 1). ^{1}H NMR (500 MHz; DMSO-d_6) of **2a** shows a singlet at δ 6.47 (s, 1H, NH, exch) accounting for one proton which indicates that methylation has taken place on N1 of **1a** to give product **2a**.The structure of product **2a** is fully supported by IR, ^{1}H NMR and FAB-MS spectral data reported in Table 1. Similarly other *N*-methyl derivatives of amidines (**2b–i**, Scheme 1) were synthesized. Physical constants and spectral data of **2b–i** are reported in Table 1.

Again when compound **1a** was treated with oxalyl chloride using dry THF as a solvent of the reaction, after usual work up of the reaction compound **3a** (Scheme 1) was obtained in good yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **3a** does not show



Scheme 1. Synthesis of *N*-methylpicolinamidine (**2a–f**), *N*-methylpyrazine-2-carboxamidine (**2g–i**) and dihydroimidazol-1-yl benzenesulfonamide (**3a–i**) derivatives.

Table 1
Physical, spectral and analytical data of **2a–i** and **3a–i**

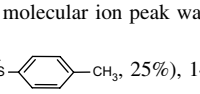
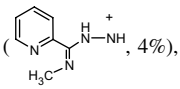
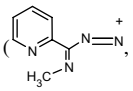
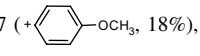
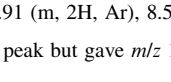
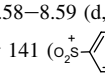
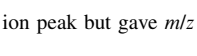
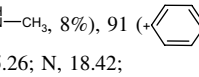
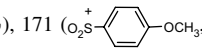
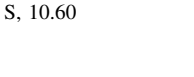
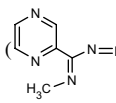
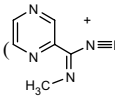
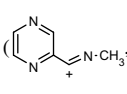
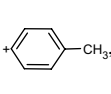
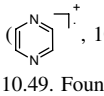
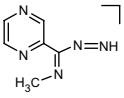
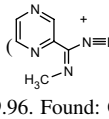
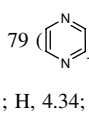
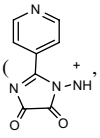
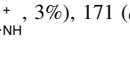
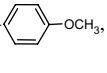
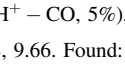
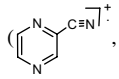
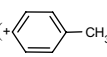
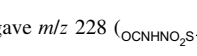
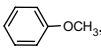
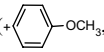
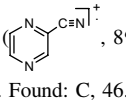
Compund no.	Solvent of crystallization/ elution	m.p. (°C)	Yield%	Spectral and analytical data: IR (KBr) cm^{-1}. ^1H NMR, FAB-MS, EI-MS, ESI-MS, GC–MS (*m/z*; relt int%)
2a	EtOAc/$CHCl_3$	100	33	IR (KBr) ν_{max}: 3495 and 3368 (–NH–NH–), 1641 (C=N), 1590 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.36 (s, 3H, $-CH_3$), 2.65 (s, 3H, CH_3), 6.47 (s, 1H, NH, exch), 7.13 (s, 1H, NH, exch), 7.39–7.54 (m, 3H, Ar), 7.75–7.94 (m, 4H, Ar), 8.54–8.63 (d, 1H, Ar). FAB-MS *m/z* 305 (MH^+, 5%). Anal. Calcd for $C_{14}H_{16}SN_4O_2$: C, 55.26; H, 5.26; N, 18.42; S, 10.52. Found: C, 55.33; H, 4.89; N, 18.11; S, 10.82
2b	EtOAc/$CHCl_3$	140	49	IR (KBr) ν_{max}: 3495 and 3369 (–NH–NH–), 1637 (C=N), 1594 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.64 (s, 3H, $-CH_3$), 3.88 (s, 3H, OCH_3), 6.44 (br s, 1H, NH), 7.10–7.12 (br d, 1H, NH), 7.19–7.20 (d, 2H, Ar), 7.53–7.56 (t, 1H, Ar), 7.80–7.84 (t, 2H, Ar), 7.87–7.91 (q, 1H, Ar), 7.95–7.97 (d, 1H, Ar), 8.63–8.64 (d, 1H, Ar). GC–MS molecular ion peak was not observed but some other fragment peaks were present, i.e. *m/z* 171 ( , 25%), 149 ( , 4%), 147 ( , 8%), 107 ( , 18%), 78 ( , 18%). Anal. Calcd for $C_{14}H_{16}SN_4O_3$: C, 52.50; H, 5.00; N, 17.50; S, 10.00. Found: C, 52.82; H, 4.68; N, 17.27; S, 9.87
2c	EtOAc/$CHCl_3$	100	49	IR (KBr) ν_{max}: 3473 and 3356 (–NH–NH–), 1635 (C=N), 1577 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$) δ: 2.81 (s, 3H, $-CH_3$), 6.50 (br s, 2H, –NH–NH–, exch), 7.45 (m, 1H, Ar), 7.65 (m, 3H, Ar), 7.75 (m, 1H, Ar), 7.90–8.20 (m, 3H, Ar), 8.54 (m, 1H, Ar). FAB-MS *m/z* 291 (MH^+, 100%). Anal. Calcd for $C_{13}H_{14}SN_4O_2$: C, 53.79; H, 4.82; N, 19.31; S, 11.03. Found: C, 53.91; H, 4.70; N, 19.58; S, 10.69
2d	EtOAc/$CHCl_3$	160	47	IR (KBr) ν_{max}: 3434 and 3356 (–NH–NH–), 1652 (C=N), 1598 and 1540 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.65 (s, 3H, $-CH_3$), 6.61 (s, 1H, NH, exch), 7.33 (br s, 1H, NH), 7.58–7.70 (m, 4H, Ar), 7.73–7.76 (t, 1H, Ar), 7.86–7.91 (m, 2H, Ar), 8.58–8.59 (d, 1H, Ar), 8.65–8.66 (d, 1H, Ar). GC–MS does not give M^+ ion peak but gave *m/z* 141 ( , 55%), 78 ( , 33%), 77 ( , 100%). Anal. Calcd for $C_{13}H_{14}SN_4O_2$: C, 53.79; H, 4.82; N, 19.31; S, 11.03. Found: C, 53.59; H, 4.72; N, 19.50; S, 11.40
2e	EtOAc/$CHCl_3$	180	33	IR (KBr) ν_{max}: 3447 and 3364 (–NH–NH–), 1642 (C=N), 1600 and 1547 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.07 (s, 3H, $-CH_3$), 2.27 (s, 3H, $-CH_3$), 6.58 (s, 1H, NH, exch), 7.09–7–11 (d, 2H, Ar), 7.38–7.40 (d, 2H, Ar), 7.78–7.80 (d, 2H, Ar), 8.57–8.58 (d, 2H, Ar), 9.42 (s, 1H, NH, exch). GC–MS does not give molecular ion peak but gave *m/z* 184 ( , 4%), 155 ( , 25%), 121 (, 8%), 91 (, 85%), 78 (, 8%). Anal. Calcd for $C_{14}H_{16}SN_4O_2$: C, 55.26; H, 5.26; N, 18.42; S, 10.52. Found: C, 54.80; H, 5.24; N, 18.11; S, 10.35
2f	EtOAc/$CHCl_3$	195	46	IR (KBr) ν_{max}: 3432 and 3350 (–NH–NH–), 1654 (C=N), 1596 and 1544 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.62 (s, 3H, $-NCH_3$), 3.87 (s, 3H, OCH_3), 6.55 (s, 1H, NH), 7.11–7.13 (d, 1H, Ar), 7.17–7.19 (d, 1H, Ar), 7.28 (br s, 1H, NH), 7.59–7.60 (d, 1H, Ar), 7.69–7.71 (d, 1H, Ar), 7.78–7.83 (q, 2H, Ar), 8.60 (d, 1H, Ar), 8.68 (d, 1H, Ar). GC–MS does not give molecular ion peak but gave *m/z* 199 ( , 2%), 171 (, 35%), 107 (, 38%), 78 (, 13%). Anal. Calcd for $C_{14}H_{16}SN_4O_3$: C, 52.50; H, 5.00; N, 17.50; S, 10.00. Found: C, 52.93; H, 5.15; N, 17.50; S, 9.83
2g	EtOAc/$CHCl_3$	160	72	IR (KBr) ν_{max}: 3442 and 3316 (–NH–NH–), 1662 (C=N), 1593 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.68 (s, 3H, $-CH_3$), 7.30 (s, 2H, NH–NH, exch), 7.61–7.77 (m, 3H, Ar), 7.89–7.93 (t, 2H, Ar), 8.71 (s, 1H, Ar), 8.79 (s, 1H, Ar), 9.08 (s, 1H, Ar). FAB-MS *m/z* 292 (MH^+, 100%), 261 ( , 13%). Anal. Calcd for $C_{12}H_{13}SN_5O_2$: C, 49.48; H, 4.46; N, 24.05; S, 10.99. Found: C, 49.81; H, 4.05; N, 24.08; S, 10.60

Table 1 (*continued*)

Compund no.	Solvent of crystallization/ elution	m.p. (°C)	Yield%	Spectral and analytical data: IR (KBr) cm^{-1}. ^1H NMR, FAB-MS, EI-MS, ESI-MS, GC–MS (*m/z*; relt int%)
2h	MeOH/EtOAc	240	48	IR (KBr) ν_{max}: 3430 (–NH–NH–), 1658 (C=N) and 1560 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.35 (s, 3H, $-CH_3$), 2.55 (s, 3H, N$-CH_3$), 6.55 (br s, 1H, NH, exch,), 7.40 (d, 2H, Ar), 7.85 (d, 2H, Ar), 8.65 (d, 1H, Ar), 8.78 (d, 1H, Ar). 9.02 (s, 1H, Ar), 9.69 (s, 1H, NH, exch). GC–MS does not give M^+ ion peak but gave *m/z* 150 ( , 1.78%), 149 ( , 25.86%), 148 ( , 74.31%), 120 ( , 5.00%), 105 ( , 3.59%), 91 ( , 2.75%), 80 ( , 100%), 79 ( , 24.04%). Anal. Calcd for $C_{13}H_{15}SN_5O_2$: C, 51.14; H, 4.91; N, 24.05; S, 10.49. Found: C, 51.02; H, 4.51; N, 24.51; S, 10.19
2i	EtOAc/$CHCl_3$	205	62	IR (KBr) ν_{max}: 3419 and 3303 (–NH–NH–), 1638 (C=N), 1589 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.66 (s, 3H, $-NCH_3$), 3.82 (s, 3H, OCH_3), 7.14–7.24 (t, 4H, 2H exch, 2H Ar), 7.82–7.86 (t, 2H, Ar), 8.71–8.72 (q, 1H, piperazine), 8.79–8.80 (d, 1H, piperazine), 9.10–9.11 (d, 1H, piperazine). GC–MS does not give M^+ ion peak but gave other peaks, i.e. *m/z* 149 ( , 10%), 148 ( , 50%), 79 ( , 15%). Anal. Calcd for $C_{13}H_{15}SN_5O_3$: C, 48.59; H, 4.67; N, 21.80; S, 9.96. Found: C, 48.81; H, 4.34; N, 21.95; S, 9.84
3a	MeOH/EtOAc	200	48	IR (KBr) ν_{max}: 3260 (–NH–), 1701 (>C=O), 1637 (C=N), 1598 and 1555 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.41 (s, 3H, CH_3), 7.44–7.46 (d, 2H, Ar), 7.72–7.73 (d, 1H, Ar), 7.81–7.83 (d, 2H, Ar), 8.07 (s, 2H, Ar), 8.75–8.76 (d, 1H, Ar), 10.84 (br s, 1H, NH, exch). FAB-MS *m/z* 345.0 (MH^+, 70%), 329 ($M^+ - CH_3$, 5%), 287.3 ($MH^+ - O{=}C{=}C{=}O^{]+\bullet}$, 14%). Anal. Calcd for $C_{15}H_{12}SN_4O_4$: C, 52.32; H, 3.48; N, 16.27; S, 8.30. Found: C, 52.01; H, 3.75; N, 16.07; S, 8.00
3b	MeOH/EtOAc	200	42	IR (KBr) ν_{max}: 3505 (–NH–), 1689 (>C=O) and 1595 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.87 (s, 3H, OCH_3), 7.20–7.22 (d, 2H, Ar), 7.60–7.62 (m, 1H, Ar), 8.01–8.09 (m, 4H, Ar), 8.60–8.69 (d, 1H, Ar), 12.27 (br s, 1H, NH, exch). FAB-MS *m/z* 361 (MH^+, 1%), 345 ($M^+ - CH_3$, 70%), 329 ($M^+ - {}^{\bullet}OCH_3$, 5%). Anal. Calcd for $C_{15}H_{12}SN_4O_5$: C, 50.00; H, 3.33; N, 15.55; S, 8.88. Found: C, 50.43; H, 3.68; N, 15.95; S, 8.70
3c	MeOH/EtOAc	140	58	IR (KBr) ν_{max}: 3465 (–NH–), 1698 (>C=O), 1625 (C=N) and 1582 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$) δ: 7.56–7.71 (m, 4H, Ar), 7.92–8.06 (m, 3H, Ar), 8.64–8.70 (q, 2H, Ar), 9.98 (br s, 1H, NH, exch). Anal. Calcd for $C_{14}H_{10}SN_4O_4$: C, 50.90; H, 3.03; N, 16.96; S, 9.69. Found: C, 50.45; H, 3.00; N, 16.86; S, 9.93
3d	MeOH/EtOAc	220	41	IR (KBr) ν_{max}: 3426 (–NH–), 1665 (>C=O), 1634 (C=N) and 1603 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$) δ: 7.54–7.67 (m, 3H, Ar), 7.98–7.99 (t, 2H, Ar), 8.18–8.21 (d, 2H, Ar), 8.82–8.84 (d, 2H, Ar), 10.5–11.0 (br s, 1H, NH, exch). FAB-MS *m/z* 331 (MH^+, 4%). Anal. Calcd for $C_{14}H_{10}SN_4O_4$: C, 50.90; H, 3.03; N, 16.96; S, 9.69. Found: C, 51.22; H, 2.87; N, 17.05; S, 9.25
3e	MeOH/EtOAc	255	49	IR (KBr) ν_{max}: 3437 (–NH–), 1688 (>C=O), 1632 (C=N) and 1488 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 7.34–7.37 (d, 2H, Ar), 7.80–7.83 (d, 2H, Ar), 8.43 (s, 2H, Ar), 9.09 (s, 2H, Ar). 9.90 (br s, 1H, NH, exch). FAB-MS *m/z* 345.0 (MH^+, 1%). Anal. Calcd for $C_{15}H_{12}SN_4O_4$: C, 52.32; H, 3.48; N, 16.27; S, 9.30. Found: C, 52.05; H, 3.30; N, 16.15; S, 9.36
3f	MeOH/EtOAc	140	64	IR (KBr) ν_{max}: 3443 (–NH–), 1681 (>C=O) and 1595 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.88 (s, 3H, OCH_3), 7.13–7.14 (d, 2H, Ar), 7.88–7.89 (d, 2H, Ar), 7.94 (s, 2H, Ar), 8.89–8.90 (d, 2H, Ar), 10.61 (br s, 1H, NH, exch). GC–MS does not give ion peak, but gave *m/z* 189 ( , 3%), 171 ( , 30%), 107 ( , 27%). Anal. Calcd for $C_{15}H_{12}SN_4O_5$: C, 50.00; H, 3.33; N, 15.55; S, 8.88. Found: C, 50.30; H, 3.70; N, 15.20; S, 8.80
3g	MeOH/EtOAc	200	81	IR (KBr) ν_{max}: 3399 (–NH–), 1695 (>C=O) and 1622, 1470 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$) δ: 7.56–7.67 (m, 2H, Ar), 7.99–8.00 (dd, 1H, Ar), 8.66–8.76 (m, 2H, Ar), 8.83–8.84 (d, 1H, Ar), 9.36–9.37 (d, 1H, Ar), 9.51–9.52 (d, 1H, Ar). FAB-MS *m/z* 332 (MH^+, 20%), 304 ($MH^+ - CO$, 5%), 141 ( , 8%). Anal. Calcd for $C_{13}H_9SN_5O_4$: C, 47.12; H, 2.71; N, 21.14; S, 9.66. Found: C, 47.31; H, 3.04; N, 21.04; S, 9.86

(*continued on next page*)

Table 1 (*continued*)

Compund no.	Solvent of crystallization/ elution	m.p. (°C)	Yield%	Spectral and analytical data: IR (KBr) cm^{-1}. ^1H NMR, FAB-MS, EI-MS, ESI-MS, GC–MS (*m/z*; relt int%)
3h	MeOH/EtOAc	145	38	IR (KBr) ν_{max}: 3469 (–NH–), 1697 (>C=O), 1632 (C=N) and 1538 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$) δ: 2.44 (s, 3H, CH_3), 7.33–7.36 (d, 2H, Ar), 7.92–7.95 (d, 2H, Ar), 8.66 (s, 1H, Ar), 8.82–8.83 (d, 1H, Ar), 9.54 (s, 1H, Ar), 10.90 (br s, 1H, NH, exch). FAB-MS does not give MH^+ ion peak but gave *m/z* 155 (, 30%), 105 ( , 9%), 91 ( , 15%). Anal. Calcd for $C_{14}H_{11}SN_5O_4$: C, 48.69; H, 3.18; N, 20.28; S, 9.27. Found: C, 48.31; H, 3.17; N, 19.87; S, 9.63
3i	MeOH/EtOAc	260	55	IR (KBr) ν_{max}: 3468 (–NH–), 1697 (>C=O), 1630 (C=N) and 1600 (Ar) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.65 (s, 3H, OCH_3), 6.86–6.87 (d, 2H, Ar), 7.67–7.68 (d, 2H, Ar), 8.59–8.60 (d, 1H, Ar), 8.72–8.73 (d, 1H, Ar), 8.99 (s, 1H, Ar), NH was not observed. EI-MS does not give H^+ ion peak but gave *m/z* 228 (, 2%), 227 (228 – H, 11%), 171 ( , 4%), 121 (228 –  , 13%), 107 ( , 9%), 105 ( , 8%), 79 ( , 34%). Anal. Calcd for $C_{14}H_{11}SN_5O_5$: C, 46.53; H, 3.04; N, 19.39; S, 8.86. Found: C, 46.91; H, 2.94; N, 19.70; S, 8.68

any peak at δ 6.47 (which was present in the starting material **1a**). This observation indicates that oxalyl chloride reacted with N1 and N2 of **1a** to give product **3a**, i.e. *N*-(4,5-dioxo-2-(pyridin-2-yl)-4,5-dihydroimidazol-1-yl)-4-methylbenzenesulfonamide. Structure of compound **3a** is further supported by correct IR, ^1H NMR, FAB-MS and elemental analysis reported in Table 1. Similarly were synthesized other dioxoimidazol derivatives (**3b–i**; Scheme 1). Physical constants and spectral data of **3b–i** are reported in Table 1.

In literature there are several examples available where pyridine and pyrazine derivatives [27–33] have shown potent anti-inflammatory activity. Hence it is considered worthwhile to screen these compounds for anti-inflammatory and analgesic activities.

2.2. Biological results

Anti-inflamamtory activity screening [34] of compounds **2a**, **3f** at 100 mg/kg p.o. and **2b**, **2d–g**, **2i**, **3a**, **3b**, **3d**, **3g**, **3i** at 50 mg/kg p.o. was carried out using carrageenan-induced paw oedema model and results are summarized in Table 2. Compounds **2a**, **3f** (at 100 mg/kg p.o.) and **2b**, **2d–g**, **2i**, **3a**, **3b**, **3d**, **3g**, **3i** (at 50 mg/kg p.o.) showed 20%, 12%, 34%, 16%, 44%, 21%, 11%, 20%, 31%, 20%, 37%, 25% and 13% activity whereas the standard drug phenylbutazone exhibited 58% (at 100 mg/kg p.o.) and 37% (at 50 mg/kg p.o.) anti-inflammatory activity. Compound **2e** exhibited anti-inflammatory activity better than the standard drug. Compounds **2a**, **3f** (at 100 mg/kg p.o.) and **2b**, **2d–g**, **2i**, **3a**, **3b**, **3d**, **3g**, **3i** (at 50 mg/kg p.o.) on analgesic activity [35] evaluation using acetic acid writhing assay exhibited 75%, 75%, 20%, 7%, 17%, 13%, 11%, 16%, 60%, 18%, 60%, 30% and 12% activity whereas the standard drug phenylbutazone showed 58% (at 100 mg/kg p.o.) and 40% (at 50 mg/kg p.o.) analgesic activity (Table 2) .Compounds **2a**, **3a**, **3d** and **3f** exhibited analgesic activity better than phenylbutazone. Compound **3d** exhibited anti-inflammatory activity comparable to and analgesic activity better than phenylbutazone.

2.2.1. Structure–activity relationship

A look at Table 2 indicates that in case of *N*-methyl derivatives of amidines replacement of 2-pyridyl or 2-pyrazinyl group by 4-pyridyl was found to be beneficial for anti-inflammatory activity and similarly a substitution by $-CH_3$ on phenyl ring increased the electron richness of the phenyl ring and hence was found useful for increasing anti-inflammatory activity, i.e compound **2e**. When CH_3 group on phenyl ring was replaced by $-OCH_3$ there is decrease in anti-inflammatory and analgesic activities. This could be due to change in electron richness of phenyl ring and steric crowding. Compound **2a** exhibited good analgesic activity and any change in phenyl ring or of 2-pyridyl to 4 pyridyl or 2-pyrazinyl decreased the analgesic activity. Again in case of cyclized compounds, i.e **3a–i**, 4-pyridyl derivatives exhibited better anti-inflammatory activity as compared to 2-pyridyl or 2-pyrazinyl derivatives. In short 4-pyridyl derivatives exhibit better anti-inflammatory activity as compared to 2-pyridyl or 2-pyrazinyl derivatives.

3. Conclusion

A series of substituted *N*-methylisonicotinamidine (**2a–f**), *N*-methylpyrazine-2-carboxamidine (**2g–i**) derivatives and dihydroimidazolylbenzenesulfonamide derivatives (**3a–i**) have been synthesized and screened for anti-inflammatory and analgesic activities. Compound **3d** exhibited anti-inflammatory activity comparable to and analgesic activity better than phenylbutazone.

4. Experimental

4.1. General

Melting points (m.p) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600FT Spectrometer. ^1H NMR were recorded on a Bruker WH-300/Bruker AV-500 Spectrometer in a ca.

5–15% (w/v) solution in appropriate deuterated solvent. FAB-MS was recorded on a Jeol SX-120 (FAB) Spectrometer. GC–MS was recorded on Perkin Elmer Clarus 500 Mass Spectometer. Thin-layer chromatography (TLC) was performed by using silica gel G for TLC (Merck) and spots were visualized by iodine vapours or by irradiation with UV light (254 nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh). Elemental analysis was performed using a Vario EL III elemental analyzer. Physical constants, spectral and analytical data of all the compounds **2a–i** and **3a–i** synthesized are reported in Table 1.

4.2. General procedure for the synthesis of *N*-methylpicolinamidine (**2a–f**) and *N*-methylpyrazine-2-carboxamidine (**2g–i**) derivatives

4.2.1. Synthesis of N^1-methyl-*N*-(4-methylphenylsulfonamido)picolinamidine (**2a**)

Amidine derivative [24] **1a** (0.290 g; 1 mmol) was dissolved in methanol (5 ml), to it were added triethylamine (0.1 ml; 1 mmol) and methyl iodide (0.1 ml; 1.5 mmol). The reaction contents were stirred at room temperature for 2 h. Solvent was removed under reduced pressure and to the residue left behind was added distilled water (5 ml) and the product was extracted with ethylacetate. Ethylacetate extract was dried over sodium sulphate (5 g). The organic solvent was removed under reduced pressure to give an oily mass. This oily mass was washed with diethyl ether (3 × 5 ml) to give crude product, which was purified by crystallization from EtOAc/$CHCl_3$ to give pure product **2a**.

Similarly were synthesized compounds *N*-(4-methoxyphenylsulfonamido)-N^1 methylpicolinamidine (**2b**), N^1-methyl-*N*-(phenylsulfonamido)picolinamidine (**2c**), N^1-methyl-*N*-(phenylsulfonamido)isonicotinamidine (**2d**), N^1-methyl-*N*-(methylphenylsulfonamido)isonicotinamidine (**2e**), *N*-(4-methoxyphenylsulfonamido)-N^1-methylisonicotinamidine (**2f**), N^1-methyl-*N*-(phenylsulfonamido)pyrazine-2-carboxamidine (**2g**), N^1-methyl-*N*-(4-methylphenylsulfonamido)pyrazine-2-carboxamidine (**2h**) and *N*-(4-methoxyphenylsulfonamido)-N^1-methylpyrazine-2-carboxamidine (**2i**).

4.3. General procedure for synthesis of dihydroimidazol-1-yl benzenesulfonamide derivatives (**3a–i**)

4.3.1. *N*-(4,5-Dioxo-2-(pyridin-2-yl)-4,5-dihydroimidazol-1-yl)-4-methylbenzene sulfonamide (**3a**)

Amidine derivative [24] **1a** (0.290 g; 1 mmol) was dissolved in dry THF (10 ml) and to it was added potassium carbonate (0.414 g; 3 mmol). The reaction mixture was cooled in an ice bath and then oxalyl chloride (0.1 ml; 1.2 mmol) was added dropwise while the reaction contents were stirred continuously. After complete addition of oxalyl chloride it was further stirred at room temperature for 1 h. The solid product that separated out was filtered and then dissolved in methanol to remove insoluble potassium salts. Solvent from the clear methanol solution was removed under reduced pressure to give crude product which was further purified by crystallization from MeOH/EtOAc to give pure product **3a**.

Similarly were synthesized compounds *N*-(4,5-dioxo-2-(pyridin-2-yl)-4,5-dihydroimidazol-1-yl)-4-methoxybenzenesulfonamide (**3b**), *N*-(4,5-dioxo-2-(pyridin-2-yl)-4,5-dihydroimidazol-1-yl)benzenesulfonamide (**3c**), *N*-(4,5-dioxo-2-(pyridin-4-yl)-4,5-dihydroimidazol-1-yl)benzenesulfonamide (**3d**), *N*-(4,5-dioxo-2-(pyridin-4-yl)-4,5-dihydroimidazol-1-yl)-4-methyl benzenesulfonamide (**3e**), *N*-(4,5-dioxo-2-(pyridin-4-yl)-4,5-dihydroimidazol-1-yl)-4-methoxybenzenesulfonamide (**3f**), *N*-(4,5-dioxo-2-(pyrazin-2-yl)-4,5-dihydroimidazol-1-yl)benzene sulfonamide (**3g**), *N*-(4,5-dioxo-2-(pyrazin-2-yl)-4,5-dihydroimidazol-1-yl)-4-methylbenzenesulfonamide (**3h**) and *N*-(4,5-dioxo-2-(pyrazin-2-yl)-4,5-dihydroimidazol-1-yl)-4-methoxybenzenesulfonamide (**3i**).

4.4. Anti-inflammatory activity

Paw oedema inhibition test was performed on albino rats of Charles Foster strain by adopting the method of Winter et al. [34]. Groups of five animals of both sexes (body weight 120–160 g), excluding pregnant females, were given a dose of a test compound. After 30 min, 0.20 ml of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1–3 h later. The mean increase of paw volume at each time interval was compared with that of control group (five rats treated with carrageenan, but not with test compounds) at the same time intervals and percent inhibition values were calculated by the formula given below.

$$\%\ \text{Anti-inflammatory activity} = [1 - D_t/D_c] \times 100$$

D_t and D_c are paw volumes of oedema in tested and control groups, respectively.

Anti-inflammatory activity of compounds **2a**, **2b**, **2d–g**, **2i**, **3a**, **3b**, **3d**, **3f**, **3g** and **3i** screened is reported in Table 2.

4.5. Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Davis et al. [35]. Groups of five mice (body weight 20–30 g) of both sexes, excluding pregnant females, were given a dose of a test compound. After 30 min, the animals were injected intraperitoneally with 0.25 ml/mouse of 0.5% acetic acid solution and writhes were counted during the following 60 min. The mean number of writhes for each experimental group and percent decrease compared with control group (five mice not treated with test compounds) were calculated. Compounds **2a**, **2b**, **2d–g**, **2i**, **3a**, **3b**, **3d**, **3f**, **3g** and **3i** were screened for analgesic activity and results are reported in Table 2.

Table 2
Anti-inflammatory activity and analgesic activity evaluation of compounds **2a**, **2b**, **2d–g**, **2i**, **3a**, **3b**, **3d**, **3f**, **3g** and **3i**

Compounds tested	Anti-inflammatory activity		Analgesic activity	
	Dose (mg/kg p.o.)	Activity (%)	Dose (mg/kg p.o.)	Activity (%)
2a	100	12	100	75
2b	50	20	50	20
2d	50	16	50	7.0
2e	25	27	25	9.0
	50	44	50	17
	100	56	100	33
2f	50	21	50	13
2g	50	11	50	11
2i	50	20	50	16
3a	50	31	50	60
3b	50	20	50	18
3d	50	37	50	60
3f	100	34	100	75
3g	50	25	50	30
3i	50	13	50	12
Phenylbutazone	25	19	25	24
	50	37	50	40
	100	58	100	58

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